ANALYSIS OF PROGRAM ACTIVITIES
NATIONAL INSTITUTES OF HEALTH
1956

NATIONAL INSTITUTE OF
NEUROLOGICAL DISEASES AND BLINDNESS

NATIONAL INSTITUTES OF HEALTH
PUBLIC HEALTH SERVICE
U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Library, Acquisitions Unit
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Blindness. Report of program activities

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-OD-1
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Office of the Director
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Administration
PROJECT TITLE

7. Pearce Bailey, M. D., Director
PRINCIPAL INVESTIGATOR

8. Assistant to the Director, Dr. Henry A. Imus; Admin. Officer, Mr. Eckart Wipf
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Similar to other Institutes.

10. PROJECT DESCRIPTION

This project concerns the office of the Institute Director and his immediate staff for the overall program direction and administration of NINDB.

The summary statement of the Institute's program has been divided into three major segments, and appear on separate statements at the beginning of project descriptions for Clinical Research, Basic Research, and Extramural Programs.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-OD-1
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$80,000	$16,924	$96,924	2	8	10

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	8	10	

13. BUDGET ACTIVITY:

RESEARCH ☐
REVIEW & APPROVAL ☐
BIOLOGIC STANDARDS ☐
ADMINISTRATION ☒
PROFESSIONAL & TECHNICAL ASSISTANCE ☐

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-OD-1
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Dr. Pearce Bailey:

Multiple Sclerosis, Postgraduate Medicine, Vol. 20, No. 3, September 1956.

Needs in Nrurology, Symposium on Training in Clinical Neurology (in press).

Neurologic Rehabilitation, Chapt. in Modern Treatment of Neurology, C. V. Mosby, publisher. (in press)

Introduction for three neurological textbooks.

Neurological and Psychological Deficits of Asphyxia Neonatorum, Charles C. Thomas, publisher (in press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Dr. Pearce Bailey:

Citation for providing outstanding leadership in the field of Public Health. By National Foundation for Muscular Dystrophy, Gotham Chapter, May 5, 1956

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-OD-2
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Cerebral Palsy Project
LABORATORY, BRANCH, OR DEPARTMENT

4. Medical Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Collaborative Study of Cerebral Palsy, Mental Retardation, and other Neurological Deficits of Infancy and Childhood.
PROJECT TITLE

7. Pearce Bailey, M. D.
PROGRAM DIRECTOR

Henry A. Imus, Ph.D.
PROJECT DIRECTOR

8. G. Milton Shy, M.D., Maitland Baldwin, M.D., Anatole S. Dekaban, M.D., William F. Windle, Ph.D., (Drs. George W. Anderson, Nicholson J. Eastman, Johns Hopkins Hospital, Consultants)
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

NINDB-3	NINDB-35(C)	NINDB-69(C)
NINDB-22	NINDB-44(C)	NINDB-70(C)
NINDB-31(C)	NINDB-65(C)	NINDB-71(C)
NINDB-33(C)	NINDB-66(C)	NINDB-93(C)
NINDB-34(C)	NINDB-67(C)	

10. PROJECT DESCRIPTION:

Objectives: To discover and/or evaluate genetic and environmental factors of etiological significance in cerebral palsy, mental retardation, and other neurological deficits of infancy and childhood. By means of collaborative field investigations, as well as intramural studies, to correlate the clinical findings of brain damaged patients with subsequent pathological findings obtained at autopsy.

Methods Employed: This study will be conducted in two ways. (1) Collaborating institutions will select pregnant mothers and/or infants showing signs of stress at birth, or showing neurological symptoms in the postnatal period. The detailed prenatal, natal, and postnatal data on these cases and the normal control cases will be collected, and the individuals will be studied clinically. Less detailed information will be obtained on the immediate family of each subject used in the study. In the event of death, an autopsy will be performed and the intact brain and spinal cord, or representative microscopic sections, will be sent to the NINDB together with the complete records on the case for further study and analysis. These findings will be collated with data on cases submitted by other collaborating institutions. Complete records will be made by the NINDB to each collaborator. (2) In certain collaborating institutions having custodial care of brain damaged patients, intensive clinical studies will be made, and efforts will be made to collect perinatal histories. When these cases come to autopsy, the intact brain and spinal cord, or representative microscopic sections, will be sent to the NINDB for further study and for clinicopathologic correlations.

Each participant will be completely free to do as much of the analyses of his own material as he desires and to publish his reports independently. The analyses prepared by this Institute will be submitted to the participants, and a statistical report of the results of all of the work will be published and distributed by the central laboratory.

Patient Material: Patients will be studied at the Clinical Center of the National Institutes of Health and at collaborating institutions in various parts of the United States. The brain damaged patients will be admitted to the study as soon as possible after the diagnosis has been made.

Major Findings: With many and variously trained personnel collecting information and pathological material, it is essential that a carefully prepared protocol be developed for the collection of patient's histories, clinical data, and pathological specimens. To accomplish this, a panel of consultants was appointed, representing various fields of medicine, including embryology, neurology, pathology, neuropathology, psychology, obstetrics, pediatrics, and orthopedics.

The protocol includes requirements for information on family history, mother's history, the record of events at birth, clinical history, the record of clinical examinations, psychological and sociological data, and a complete record of pathological examinations, including specific details for the removal, sectioning, and preservation of the brain and spinal cord. This protocol is now being subjected to practical test at certain institutions. Concurrently the research potential of selected medical centers has been surveyed and institutions which might collaborate in the study have been invited to submit proposals for consideration by the National Advisory Neurological Diseases and Blindness Council.

Two proposals have already been approved to initiate programs at Yale University Medical School and Brown University with the collaboration of local hospitals and local voluntary groups.

A new Advisory Committee, of which the Program Director of each collaborating institute is a member, and through which the various scientific disciplines are well represented, has been appointed to advise on the research design and standard protocol to be followed. This Advisory Committee will meet from time to time to resolve problems of standard procedure and advise in establishing policies with respect to the conduct of research.

Significance to the Program of the Institute: It is anticipated that the increased understanding of the etiology and the clinicopathologic correlations gained by this study will lead to better terminology, classification, prophylaxis, and treatment in the field of cerebral palsy. Furthermore, this investigation should provide valuable leads for future research in this field.

Proposed Course of Project: After the protocol has been given further preliminary trial, and more collaborating institutions have initiated programs, the collection of data and autopsy material will begin.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-OD-2
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$59,000	$10,182	$69,182	1	2	3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Yale University School of Medicine, New Haven, Conn.
Brown University, Providence, Rhode Island
Duke University, Durham, North Carolina
Johns Hopkins University, Baltimore, Maryland

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-OD-2
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Anderson, George W., M.D., "A Comprehensive Attack on Cerebral Palsy" Exhibit Brochure for American Academy of Neurology Meetings, St. Louis, Missouri, April 25-28, 1956.

Bailey, C. J., Windle, W., "Possible Interrelationship of Neonatal Asphyxia, Cerebral Palsy and Mental Retardation," to be published in the proceedings of "Symposium on Metabolic Aspects of Mental Deficiency."

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-OD-3
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Office of the Director
LABORATORY, BRANCH, OR DEPARTMENT

4. Publications and Reports
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Scientific Information and Education Activities
PROJECT TITLE

7. Mr. Edward M. Glick
PRINCIPAL INVESTIGATOR

8. Mr. Frank O. Barden, Jr.; and Mr. Russell D. Bowman
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Similar to scientific information and education activities of other institutes.

10. PROJECT DESCRIPTION

It is the responsibility of this section to supervise, plan, and coordinate the collection, editing, assembly, review, clearance, presentation or dissemination of information pertaining to neurological and sensory diseases and disorders to federal departments

and agencies, voluntary and private organizations, and the general public. It is the function of this section to plan and direct an integrated information and education program directed to improving the state of public opinion regarding research into neurological and sensory disorders and, in particular, to make available to the public data on the nature of and research developments pertinent to such diseases as cerebral palsy, epilepsy, multiple sclerosis, muscular dystrophy, amyotrophic lateral sclerosis, myasthenia gravis, cerebral vascular disease, glaucoma, cataract, uveitis, deafness, and mental retardation. It is also the function of this section to provide editorial assistance to scientists in the development and processing of professional communications which are basically the responsibility of such scientists.

During fiscal 1957, an increase in workload of the Publications and Reports Section and the development of an expanding and coordinated informational program have resulted in the addition of personnel, space and facilities dedicated to that program. Informational activities underway include:

(a) development of a comprehensive pamphlet on the Institute and its programs; (b) development of fact sheets (as bases for pamphlets) on cerebral palsy, epilepsy and mental retardation; (c) consultation and guidance in the development of a film script dealing with the perinatal period in relationship to neurological disease; (d) preparation of progress reports in four areas, glaucoma and cerebral vascular disease among them; (e) development of several periodical articles directed to lay audiences with particularly emphasis on the collaborative perinatal project; (f) the development of a new exhibit directed to American Academy of Neurology meeting in Boston, April, 1957, and revision of Cerebral Palsy exhibit for use in Brussels, Belgium in July; (g) development of a coordinated program for guided tours of the Institute by interested voluntary groups; (h) development and coordination of a public information program pertaining to the published work of NINDB-supported grantees.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-OD-3
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$34,000	$8,462	$42,462		6	6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57		6	6	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-OD-3
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"A COMPREHENSIVE ATTACK ON CEREBRAL PALSY"

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

First Award (scientific exhibits section) for the exhibit "A Comprehensive Attack on Cerebral Palsy" by the American College of Obstetrics and Gynecology, Chicago, Illinois, 1956.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-OB-4
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Office of the Director
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Training
PROJECT TITLE

7. Dr. Pearce Bailey, M. D., Director
PRINCIPAL INVESTIGATOR

8. Drs. Shy, Livingston and Imus; and Mr. Eckart Wipf
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Similar to programs in NIMH and NHI.

10. PROJECT DESCRIPTION

This project is being initiated in FY'57 as result of the totally-expressed interest of the Congress in professional training. Steps are being taken to formulate policies, and to select personnel such as medical officers, basic scientists, nurses, etc., for specialized training.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-OD-4
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$50,000	$2,838	$52,838	7		7

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	7		7	

13. BUDGET ACTIVITY:

TRAINING

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-OD-5
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Biometrics Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Biometry
PROJECT TITLE

7. _____
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Similar to biometrics programs of other institutes.

10. PROJECT DESCRIPTION

This program will begin in January, 1957, with the appointment of the Chief Biometrician.

The function of the Branch will be to develop and execute a program for the collection, analysis, and interpretation of statistical data relating to the prevalence and incidence of neurological disorders and diseases of the eye and other sensory disorders and diseases.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-OD-5
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$25,000	$946	$25,946	1	1	2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	3	2	5	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-OD-6
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Office of the Director
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Field Projects
PROJECT TITLE

7. . Pearce Bailey, M. D., Director
PRINCIPAL INVESTIGATOR

8. Drs. Shy, Livingston, Seger, Imus, Baldwin, Windle, and Weissler
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Similar to field investigations programs in NCI, NHI, and NIMH.

10. PROJECT DESCRIPTION

Within the basic and clinical research programs of the Institute also are the activities which participate with and serve as a coordination center or a central laboratory for the collaborative and cooperative research projects which are undertaken by medical centers. (See Project Description, NINDB-EP-2). Through such collaborative efforts, a comprehensive, multidisciplinary attack is underway on cerebral palsy in

in which attempts will be made to correlate clinical manifestations and pathological findings to improve the classification, diagnosis, treatment, and prevention of cerebral palsy. The experimental study of perinatal factors leading to cerebral palsy and mental retardation, using pregnant and infant monkeys, is rapidly developing in the joint project with the University of Puerto Rico, in San Juan. A developmental approach to the organic causes of cerebral palsy and mental retardation, and other manifestations of brain damage is underway. Congenital anomalies are produced in animals by X-ray radiation or chemical means at various stages in pregnancy and the malformations produced are studied by gross and microscopic examinations. Parallel to this are pathological studies of human embryos, fetuses, and stillbirths obtained from cooperating hospitals in the area. A long-term study of the effect of relaxant drugs upon involuntary movements and rigidity in the cerebral palsied has been initiated. (See Project Description, NINDB-OD-2).

Similarly, collaborative and cooperative projects concerning cerebral vascular disease, epilepsy, the testing of neurosurgical procedures, deafness, and the role of the nervous system in the aging process are also being organized.

Considerable controversy exists regarding research approaches in the aging of the nervous system and problems of the aged. The present status of research to consider new leads and different approaches is being examined in order to formulate a plan for an effective study of significant factors.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-OD-6
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$225,000	$60,920	$285,920	3	3	6

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	6	6	12	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS
SUMMARY STATEMENT - EXTRAMURAL PROGRAMS
(1956 Calendar Year)

During the 1956 calendar year considerable advance has been made in meeting the central objective of increasing the amount and productivity of medical research in the neurological and sensory disease field. This objective is gained by making funds available for additional research in such a manner as to encourage productivity and by increasing the research competence of personnel by support of highly specialized training.

During the year, 575 research grants were made totaling $6,235,000 as contrasted with 422 grants in the amount of $4,463,000 the preceding year. Although these figures are merely indicative of increase in volume, this increase was accompanied by several changes in administration and programming to increase productivity concomitant with increase in volume, and also a number of significant advances were made on the research front.

Administrative Developments

As an administrative measure, the change in grant budget policy to provide investigators greater freedom in the expenditure of funds not only allows for wiser expenditure of research monies but also makes it easier for an investigator to utilize the funds granted to meet research needs as they develop in the course of his research and to meet unforseen exigencies. This change aids in making research more productive and more self-satisfying to the investigator. Another administrative development during the year was the decision to increase the administrative staff so as to provide expert guidance and emphasis on each part of the extramural program. Personnel available and suitable for administering extramural programs are difficult to acquire. One additional professional staff member has been added during the year and two more are scheduled to fill positions during the next calendar year.

Programming Developments

In programming, 1956 has proven to be exceptionally active. Early in the year, a program of postdoctoral training grants in the basic neurological sciences was inaugurated. With clinical training programs well underway and beginning to turn out highly trained clinical investigators, the need for large numbers of specially trained basic scientists to assure a coordinated research effort was becoming increasingly acute. Postdoctoral training grants in such disciplines as neurochemistry, neuropharmacology, neuroanatomy and neurophysiology will meet this need for the integration of basic and clinical research.

Another development was the establishment of a program of Field Investigations and Pilot Projects to broaden the research program base and to facilitate the support of surveys, interdisciplinary projects and broad multi-institutional cooperative and collaborative studies. This program, which at present is at the $500,000 level will probably necessitate an expenditure of over three million dollars during the next calendar year.

The 1956 calendar year also saw the initiation of the collaborative project on cerebral palsy and mental retardation. This complex investigation preceded by over two years of planning and organization, involves an important widespread medical problem, the solution of which can only be approached through a multi-institutional and multi-disciplinary effort, requiring the cooperation of a large number of clinical and basic researchers over a period of years. It is anticipated that this study in a few short years will provide a break-through in a front that has long baffled medical research.

During the latter part of the year programming also got underway to organize and carry out a large scale cooperative study on cerebral vascular diseases. The first phase of this study will involve twenty to thirty institutions teaming up to gather data on the prevention and treatment of intercranial aneurysms and acute subarachnoid hemorrhage. It is expected that this study will indicate the treatment of choice for such disorders and will also yield baseline data of considerable value to other studies in the cerebral vascular field.

Major Problems

With additional funds available for grants in research and training the problem of obtaining adequately trained personnel in sufficient numbers became more pressing and constitutes the major problem confronting the acceleration of research in the neurological and sensory disease field. This is especially noticeable in collaborative and cooperative studies which often require complete research teams, teaming with other such groups working in concert to pool data and thus obtain the information sought in the shortest possible time. Because of the paucity of well trained personnel, many otherwise outstanding institutions do not have a team of scientists who can participate in a cooperative undertaking. The training of additional clinical investigators and basic scientists will fill this need but not immediately. Training programs which started on a limited scale in 1953 are beginning to produce a scattering of specially trained individuals. Such personnel are being utilized, by and large, to complete training staffs and to start new training programs. The full impact of the training program will not be felt until 1959, by which time the results of the training expansion began in 1953 and 1954 will be apparent. It is a matter of record that at least five times as many investigators in the neurological and sensory disease field are in training today than was the case in 1952. It is believed that by 1959 it can be shown that the proportion of individuals so trained who choose full time investigative work for careers has equally increased.

Accomplishments of Special Significance to the Total Program

Although there were a number of important accomplishments by grantees during the year, in the over-all picture certain program developments will undoubtedly prove to be of signal significance.

The initiation of the collaborative project on cerebral palsy and mental retardation touches off a large scale effort in a field that regardless of its medical importance has heretofore been almost totally neglected because of its complexity. The coordinated effort of many of the leading pediatricians, obstetricians and neurologists in the country working toward a common goal is an accomplishment in itself. In this setting, future significant research accomplishments are assured.

Of the same nature and perhaps of no lesser importance is the inauguration of a large scale cooperative study of cerebral vascular diseases. Although of tremendous importance from the standpoint of human welfare, little progress has been made in this area to date through isolated effort. It is believed that establishing a situation wherein participating investigators will periodically confer with each other to work out mutual problems will result in important research developments.

Some of the outstanding advances resulting from the support of project research follow.

B-468 - Developmental lesions in the brains of infants - David B. Clark, M. D., Assistant Professor of Neurology, Johns Hopkins Medical School

Dr. Clark's work, which has been supported by an NINDB grant since 1953, is centered around determining whether or not cell changes can be discovered in the histologically less mature brain as compared with more mature brains from comparable cases. At a conservative estimate the United States annually produced about 60,000 viable infants, so handicapped as to be a continuing charge on the community throughout their lives. The large majority of these are handicapped because of CNS defects. Dr. Clark's work is directing light on the causes of neurological deficit of a type that is potentially modifiable.

B-1109 - Analysis of 50,000 electroencephalograms recorded in the waking and sleeping states - Frederic A. Gibbs, M. D., Professor of Neurology, University of Illinois

Dr. Gibbs' work is of an epidemiologic nature which is making electroencephalographic diagnosis more accurate and making electroencephalographic prognosis possible. Dr. Gibbs' work is of great aid in determining the factors of electroencephalograms that have clinical significance thereby increasing the usefulness of electroencephlography as a clinical tool. This work is especially important to such disorders as infantile spasms, petit mal, grand mal and psychomotor epilepsy.

B-361 - Quantitative Histochemical Studies of Cerebral Cortex - Alfred Pope, M. D., Associate Professor of Neuropathology, Massachusetts General Hospital

Dr. Pope was the first to make quantitative histochemical studies on the brain and has made a series of fine contributions. The cortex is still a very difficult part of the brain to study since the smallest samples which now may be analyzed still represent a combined mixture of nervous elements. His studies, by isolating DNA and RNA and making counts of various cell types has already brought some clarification to this confusing problem. He is histologically mapping the functions of various areas of the brain, primarily areas concerned with wakefulness and sleep, and ascertaining the effect of hypnotic and tranquilizing drugs. His work is providing increased understanding of the biochemical organization of the cortex as a biological unit and is also providing baseline data for comparative studies of this tissue both in the adnormal and diseased state. In addition, in his work he has succeeded in developing new micro methods which will provide additional tools to workers in tissue micro chemistry.

B-536 - Nature of the Retinal Process underlying Color Vision - Alexander Forbes, M. D., Harvard University

This study, which has been in progress since 1953, has broken new ground in yielding quantitative and meaningful approaches to problems of color vision. It is a basic research project involving the use of turtle eye, which has been extremely productive in adding new knowledge to the little that is now known relative to color blindness.

B-731 - The Cause and Mechanism of Vascular Disease of the Brain - Charles M. Fisher, Associate Neurologist, Massachusetts General Hospital

The most important phase of Dr. Fisher's work has been his study of the treatment of strokes, more specifically the effect of anticoagulatns in cerebral thrombosis. This study was activated in 1954 and since that time has been extremely productive. Cerebral vascular disease is the most common neurological disease. Any advance in this area is of major importance in the field of human welfare. Dr. Fisher's work is throwing additional light on the pathological, physiological, and neurological aspects of cerebral vascular disease, which information is being used by investigators throughout the country to advance the fund of medical knowledge in this area.

B-864 - Electrical Activity of Single Receptors and Neurones of the Eye - Haldan K. Hartline, M. D., Rockefeller Institute for Medical Research

Dr. Hartline is making an investigation of the physiology of vision by studying the electrical activity of the individual receptor cells and neurones of the eye. This study is increasing the understanding of visual processes in terms of the mechanisms of the cellular components of the visual system and their interactions. The interactions studied are of basic importance to visual physiology and to neurophysiology in general. The analysis of a simple inhibiting interaction in a primitive eye adds materially in understanding the more complex interactions in the vertebrate retina. Such information contributes to the understanding of intensity discrimination, flicker perception, movement perception, brightness contrast, border contrast and visual resolution. A NINDB grant has supported Dr. Hartline's work in this field since 1955.

B-154 - The Eye in Old Age - Abraham L. Kornzweig, M. D., Chief Ophthalmologist, The Home for Aged and Infirm Hebrews of New York City

This project has been supported by the NINDB since January 1, 1952. It is a detailed clinical and pathological study of the eye in old age and has contributed materially to our knowledge of the eye problems of an aging population. Among the chief causes of blindness in the aged are diseases of the macula and glaucoma. Postmortem examination of the eyes of over 400 residents in this institution has indicated that vascular disease of the retina is the cause of most of the adverse macular conditions occurring in this age group. This study is also adding to our fund of information necessary for the early detection and treatment of glaucoma.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-EP-1
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Extramural Programs Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Research Grants
PROJECT TITLE

7. Alfred Weissler, Ph.D.
PRINCIPAL INVESTIGATOR

8. Gordon Seger, Dr. P. H.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OR PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Research Grant Programs of all other Institutes and Divisions of the NIH.

10. PROJECT DESCRIPTION

Objective - To improve the prevention, diagnosis, and treatment of neurological and sensory diseases, by support of basic and applied research in these fields at nongovernmental institutions.

Method employed: Grants of funds are made on the basis of scientific review of applications requesting financial aid to provide salaries, equipment, supplies or other items needed in the pursuit of medical research. Applications contain a detailed description of the research planned and other data necessary to scientific evaluation. Review is performed by committees of expert consultants and recommendations made to the National Advisory Neurological Diseases and Blindness Council whose members are outstanding professional and lay leaders.

Major fields of emphasis: During the calendar year 1956, 575 research grants totaling $6,235,116 were awarded in this program. These have supported research projects conducted in 156 nonfederal research institutions throughout the country. In addition, 86 requests having an aggregate of $883,760 were received, which review committees failed to recommend for support.

Financial support was provided for a wide range of research into the causes, care, and treatment of diseases and conditions of the brain, spinal cord and peripheral nerves, sensory endings, eye, and ear. Such specific disorders as cerebral palsy, muscular dystrophy, epilepsy, multiple sclerosis, cerebral vascular accidents, mental retardation, glaucoma, cataracts, retrolental fibroplasia and other blinding eye conditions, and impairments of hearing, balance, and speech are included in projects presently active.

Significance to Neurological and Sensory Disease Research: The improved quality and quantity of fundamental and applied research, made possible by this grant program, constitutes a substantial contribution over the years towards the prevention and control of neurological and sensory disorders. Significant advances are being made, with the financial assistance provided by this program, in such fields as the determination of the exact functions of the different parts of the brain, the nature of the transmission of impulses along the nerve fibers and across the synapses, the fundamental physiology of the eye and ear, and the basic mechanisms of brain damage in the young and the old.

Proposed course of project: Financial assistance will continue to be provided for those presently active projects which may be recommended by our scientific and advisory review groups. New projects will be supported insofar as funds allow, in order that the efforts of more medical and research manpower may be brought to bear on problems in the neurological and sensory disease fields involving such disciplines as neuroanatomy, neurophysiology, neuropathology, neurobiochemistry, neurology, ophthalmology, otolaryngology, etc.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-EP-1
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS

FY'57 $7,630,000

13. BUDGET ACTIVITY:

Grants for research projects.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-EP-2
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Extramural Programs Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Field Investigations and Pilot Projects
PROJECT TITLE

7. Alfred Weissler, Ph.D.
PRINCIPAL INVESTIGATOR

8. Gordon Seger, Dr. P. H.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Is similar to Field Investigation Projects of the NCI and Community Studies Projects of the NIMH.

10. PROJECT DESCRIPTION

Objective: To facilitate and broaden investigative activity in neurological and sensory areas of relative neglect, such as cerebral palsy, mental retardation, and cerebral vascular disorders, by providing financial assistance for investigations in these areas.

Method employed: Grants are made on the basis of applications requesting funds for salaries, equipment, supplies or other items needed for carrying on the investigations. These applications contain a detailed description of the work plan and other data necessary for evaluation, and are reviewed by committees of experts in clinical and scientific fields.

Major fields of emphasis: This program was started on July 1, 1956. During the six months between that date and the end of the year, fourteen grants totaling $493,781 were awarded in this program. These have supported research projects conducted in 13 nonfederal institutions throughout the country. In addition, six other applications requesting a total of $205,291 were received, which review committees failed to recommend for support.

Among the types of projects to be supported are broad collaborative and cooperative clinical studies, surveys, developmental projects, community studies, and pilot projects of a nature that will contribute to methods and procedures for the prevention, control, diagnosis and treatment of neurological and sensory disorders in the general population.

Significance to Neurological and Sensory Disease Research: Certain disorders are of such obscure of complex etiology that significant progress can be made only by means of a large scale attack, utilizing all relevant scientific and clinical disciplines and a larger number of patients than can be found at any single institution. Among such disorders may be mentioned cerebral palsy, retrolental fibroplasia, and cerebral fascular accidents.

This program provides an effective framework for the prosecution of collaborative and cooperative multi-disciplinary projects, involving neurologists, neuropathologists, pediatricians, obstetricians, psychologists, geneticists, biochemists, neurophysiologists, etc., at ten or twenty institutions in all parts of the country, yet working under a comprehensive unified plan.

The result of such large scale undertakings are expected to advance clinical medicine in ways that are not possible under the conventional system of individual disconnected small research projects.

Proposed course of project: This program is undergoing expansion, in part as a result of congressional emphasis on the need for elucidation of the etiology of cerebral palsy and mental retardation. It is anticipated that this program will at least triple in size during calendar year 1957, in view of the large-scale collaborative project on cerebral palsy and the cooperative study of the cerebral-vascular disorders which is acquiring momentum at the end of 1956.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-EP-2
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS

FY'57 $2,000,000

13. BUDGET ACTIVITY:

GRANTS FOR RESEARCH PROJECTS

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-EP-3
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Extramural Programs Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Graduate Training Grants
PROJECT TITLE

7. Gordon H. Seger, Dr. P. H.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OR PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: To increase the number of highly trained personnel available for teaching and research positions in the broad field of neurological and sensory diseases.

Method Employed: Accredited training institutions, including teaching hospitals, may submit applications for funds to establish, expand and improve training programs in the clinical specialities and basic science disciplines pertinent to neurological and sensory diseases and in which there is a recognized dearth of adequately trained personnel. Applications are carefully reviewed by non-government consultants expert in the field of training proposed and especially chosen for their competence in medical science education. Applicants are requested to set forth in detail the program of training proposed, the nature and extent of the personnel to do the training, and the nature and extent of the training facilities. Consultants usually visit the applicant institutions to confer with the proposed training Program Director and other institutional officials before recommending the action to be taken on a request. In the evaluation of a request major emphasis is placed on ascertaining the proposed programee's potentialities for training scientific personnel for academic positions.

Major Fields of Emphasis: Training program grants are made to support clinical training in neurology, ophthalmology, otolaryngology and neuropathology, and basic science training in such disciplines as neuroanatomy and neurophysiology. A total of 108 Graduate Training Grants amounting to $2,058,190 were awarded during calendar year 1956. These grants were made to 61 training institutions located in all major sections of the country. During this period 152 applications were received, requesting $3,506,335. Of these, 70 percent were approved in amounts totalling 59 percent of the funds requested.

Significance to Neurological and Sensory Disease Research: Until recently, relatively little emphasis has been placed on solving the multitude of medical problems associated with neurological and sensory diseases and disorders. As a consequence, few basic researchers are equipped to work in this field and thus increase the amount of fundamental information available and few clinical investigators are so trained as to be able to apply at the patient level the little existing information. Only through the training of sufficient numbers of such highly specialized personnel can research progress in this complex and important field be accelerated.

Proposed Course of the Project: Support of both basic science and clinical training programs that are succeeding in carrying out the objectives of this project will be continued. The number of clinical training programs will increase as additional training institutions acquire suitable personnel and are able to take on such responsibilities. The major portion of this increase will undoubtedly be in the field of otolaryngology because of the paucity of special training programs in this area. In addition, a large increase in the number of special training programs in the basic neurological sciences is anticipated, since support of training in this area was only recently initiated and the need is great.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-EP-3
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS

FY'57 $3,250,000

13. BUDGET ACTIVITY:

TRAINING GRANTS

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-EP-3
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Gordon H. Seger, "Administration of Training Programs by the National Institute of Neurological Diseases and Blindness." NEUROLOGY Volume 6, Number 12, December 1956

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-EP-4
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Extramural Programs Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Special Clinical Traineeships
PROJECT TITLE

7. Elizabeth C. Hartman, M. S.
PRINCIPAL INVESTIGATOR

8. Gordon S. Seger, Dr. P. H.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS) IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION

Objective: To encourage clinicians already trained in a speciality to undertake additional training in the field of the neurological and sensory disorders, to qualify themselves for teaching and investigation in these complex and highly specialized areas of medical endeavor.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-EP-4
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS

FY'57 $500,000

13. BUDGET ACTIVITY:

TRAINING GRANTS

Method employed: Applications, supplemented by letters from teachers, employers, and professional associates, transcripts of academic records, and a statement of financial need from the applicant, are carefully reviewed to determine the adequacy of the candidate's professional background, his fitness and desire for a career in academic medicine, and the stipend to be recommended.

Regular Clinical Traineeships are no longer awarded; financial aid for trainees at the residency level is provided through the Graduate Training Grants to a large number of institutions. Special Clinical Traineeships carry on annual stipend ranging from $4500 to $14,800, according to the needs and qualifications of the applicant. The average paid this year was $7000. Awards are made only to candidates who have completed the residency required for certification in a specialty, and who feel the need for additional training experience in the neurological and sensory disorders area related to their specialty. For example, pediatricians apply for training in pediatric neurology, neurologists for training in neuropathology, ophthalmologists for training in physiological optics, etc.

Major fields of emphasis: During the calendar year 1956, 28 Clinical Traineeships were awarded for training at 18 institutions in the United States and at 1 foreign institution. Ten of these awards were made for special training in ophthalmology, 8 in neurology, 4 in pediatric neurology, 2 in neuropathology, and 1 each in neurosurgery, neurochemistry, neuroanatomy, and ophthalmology surgery.

Significance to Neurological and Sensory Disorder Research: The leadership of competent teachers and investigators is essential to the solution of the extraordinarily difficult, varied, and complex problems presented by the neurological and sensory disorders. Broad training background both in the clinical and related basic science fields is indispensable for the development of clinicians qualified for this role in the field of medicine. Competent clinicians are encouraged to take these important years of additional training by financial support afforded by this program.

Proposed course of project: It is proposed to continue this program, with particular attention to applications from fields in which special need for trained professional personnel exists, and with the intent of complementing the Graduate Training Grant program, in the total effort to provide highly trained, competent clinical teachers and investigators.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-EP-5
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Extramural Programs Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Research Fellowships
PROJECT TITLE

7. Elizabeth C. Hartmen, M. S.
PRINCIPAL INVESTIGATOR

8. Gordon S. Seger, Dr. P. H.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESENBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Complements Research Fellowship programs of other institutes.

10. PROJECT DESCRIPTION

Objective: To ensure a steady and continuous supply of scientists highly trained in the skills required for competence in laboratory research in the various fields of the neurological and sensory disorders.

Method employed: Awards are made to the most promising candidates, as determined by a careful review of applications and the supporting data provided by letters of reference and academic records. Awards are made for both predoctoral and postdoctoral training; in addition, a small number of special research fellowships are awarded to the more mature and experienced scientists whose research effort would be benefited by additional training in a specialized area. A number of awards are also made to part-time students. These awards, exclusive of the part-time students, averaged approximately $3400 each.

Major fields of emphasis: During the calendar year 1956, 67 fellowships were awarded, 27 of which were at the predoctoral level, 35 at the postdoctoral and 5 at the special level, paying a total of $230,246. In addition, 12 of these students received supply grants in the total amount of $4,750, and 154 part-time students recieved a total of $90,720.

Research training was undertaken in 31 institutions in the United States, 2 in Canada, 1 in England, 2 in Germany, 1 in Switzerland and 1 in Sweden. There is a wide variety in the specialized areas represented: 12 awards were made for research training in physiology; 9 in anatomy; 7 in biology; 5 in biochemistry; 4 each in chemistry, pharmacology and neurophysiology; 3 each in pathology and psychology; 2 each in ophthalmology and neurosurgery; and 1 each in neurochemistry, neuropathology, neurology, zoology, electrical engineering, enzymology, nutrition, biophysics and public health.

Significance to Neurological and Sensory Disorders Research: Scientists trained in a wide variety of highly specialized research skills are essential to providing the basic laboratory information which is the foundation for clinical investigation in the complex field of the neurological and sensory disorders; the training period required is proportionately long and expensive.

Financial support for promising young scientists in these fields is necessary so that they may not be discouraged from undertaking so difficult a program of preparations and so that progress in understanding neurological and sensory disorders may not be limited by a lack of competent investigators in the field.

Proposed course of project: It is proposed to continue this project without change in its essentials, but with more effort directed to making it complement the program of Graduate Training Grants in the Basic Sciences.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-EP-5
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS

FY'57 $500,000

13. BUDGET ACTIVITY:

RESEARCH FELLOWSHIPS

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Part A. Project Description Sheet

1. NINDB-EP-6
SERIAL NUMBER

2. National Institute of Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Extramural Programs Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Review and Approval
PROJECT TITLE

7. Gordon S. Seger, Dr. P. H.
PRINCIPAL INVESTIGATOR

8. Alfred Weissler, Ph.D., and Elizabeth Hartman, M. S.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

Similar to review and approval activities of other institutes.

10. PROJECT DESCRIPTION

This activity provides for the support of the activities of the National Advisory Council on Neurological Diseases and Blindness, the advisory training committees in neurology, ophthalmology and otology, and the professional and clerical staff engaged in the processing, analyzing and management of the grants and awards. Included within this activity are funds for the Institute's proportionate share of costs for services performed centrally by the Division of Research Grants.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-EP-6
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$179,000	$131,000	$310,000	6	13	19

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
8	15	23	

FY'57

13. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☒	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Fourth Annual Report of Clinical Investigations of the National Institute of Neurological Diseases and Blindness

1956

The Clinical Director's Report

At the time of the writing of the fourth annual report of the Clinical Investigative Unit of the National Institute of Neurological Diseases and Blindness the full time staff is now all present with the exception of three positions -- that of the neuroradiologist, the second neurologist, and the neurophysiologist. All other section chiefs now have functioning laboratories at their disposal.

Four new sections were activated during the year as per the original plan. These were: the Section of Ophthalmologic Physiology, under the direction of Dr. Michelangelo Fuortes; the Section of Ophthalmologic Histopathology , under Dr. Theodor Wanko; the Section of Experimental Pain, under Dr. Kenneth Hall; and the Section of Neuropathology vacancy has been filled, after searching for a suitable candidate for a period of eight months, by Dr. Igor Klatzo. From their previous training and reputation it is hoped that these individuals will bring much to the Institute. The majority of these projects listed herein for them will, of course, represent their projected work for the coming year.

The total number of projects in the Institute is now 99 and have, during the past year, been productive of 87 manuscripts that have been accepted for publication or have been published, 3 books, and 2 monographs.

It would be difficult indeed to indicate which unit contributed the most to the investigative program in that, in general, the quality of all units was high. Special reference, however, must be made to the organization and operation of the new ophthalmological unit under Dr. Ludwig von Sallmann, who in a period of only a year-and-one-half, has organized a branch containing 5 sections and productive of 22 manuscripts, even during its formative years. The quality of these manuscripts also are among the better produced.

The work of the Electroencephalography Branch also deserves special notation in its rapid expansion to accomodate visiting personnel who are attracted to this laboratory and who, in their short period of time with

the laboratory under the guidance of Dr. Cosimo Ajmone-Marsan, have also been productive of some outstanding work. These citations should in no way detract from the rest of the work submitted by the Institute, but merely points out the ability of these units to be productive during a period of expansion.

Only one member of the senior staff was lost to the organization during the reporting year and this was the chief of the Section of Neurophysiology who resigned due to health.

Each year the writer of this report will attempt to rotate the various branches in their order of appearance in this report to minimize personal bias in the report. More specifically, then, the projects to be reported on are as follows:

The Ophthalmology Branch of the National Institute of Neurological Diseases and Blindness: Dr. von Sallmann and his branch have been productive of many original and well documented contributions to the field of ophthalmology and to neuro-ophthalmology. The appointment of Dr. Bornschein to the laboratory of Ophthalmologic Physiology as a visiting scientist ellucidated much of the unknown in electroretinography. Associated with Dr. Bornschein were Doctors Goodman, Iser, and Gunkel. Characteristics of the electroretinogram during scotopic and photopic vision in normal, color blind, and night blind subjects proved that the "late positivity" was a scotopic B-wave and not a specific photopic red response. The response of the A, B, and X waves in this function to changing adaptation and stimulus intensities were shown to be consistent with the behavior of these waves under single flash electroretinography. The clinical importance of the ERG has now been clearly established as the result of the four published papers of these investigators and it should now be clearly possible to differentiate congenital anamolies and hereditary degenerations as well as differentiate retinal disease from disease of nerve.

Considerable effort has also been expended into the chemistry, histopathology, and response to radiation of the crystalline lens of the eye. Species variation to photons were found to be of quantitative rather than qualitative nature. This provided the basis for the extrapolation of experimental data for the human cataract change following

ionizing radiation. The latter cytologically has many similarities to the senile cataract. Dr. von Sallmann and his colleagues have concluded that certain cataractogenic agents have their action by way of injury to cell nuclei of the germinative zone, whereas others attack primarily the cytoplasm. Dr. Resnik is also studying the protein of the crystalline lens by investigation into the homogenous compounds. At least four protein derivitives have been found in the crystalline lens and further studies now as to the relative amount of RNA and DNA in the lens are being undertaken. Studies into the pathogenesis of glaucoma with emphasis on how the central system controls this function were continued during the current year by Doctors von Sallmann, Macri, and Wanko. They are continuing their systematic exploration of brain stem structures to determine the effect on intraocular pressure which might not be related to blood pressure and that which is related to blood pressure. Concurrent with these studies, various pharmacological agents are being tested and more recently, techniques have been devised by Dr. Macri to analyze the participation of the outflow mechanism of aqueous formation. Aiding in this respect is the cytological work of Dr. Holland who is extending anatomical studies of the innervation of this outflow area to further ellucidate the neural control of the outflow mechanism and, finally, in the understanding of glaucoma, Dr. Macri and Dr. Fourtes are studying the effects of the external ocular muscle tension upon intraocular pressure.

Dr. O'Rourke is continuing his study of intraorbital tumors and, in particular, melanomas. He is doing this largely through the utilization of unstable isotopes, in particular P-32, and by utilization S-91 mouse melanoma. Previous workers have indicated that P-32 could be of use in detection of posterior orbital neoplasia. Dr. O'Rourke's careful studies seem to show that this is beyond the limits of the physical characteristics of this isotope and he is now turning to Iodine-131 and Zn-69.

A sufficient number of cases have now been acquired by this branch to undertake a systematic evaluation of steroid therapy in patients with uveitis. Over 300 patients with this disease have been studied over the past three years including the time that Dr. Hart and Dr. Ryan were also in the unit. In regard to uveitis, Dr. O'Connor has been studying precipitating antibodies in toxoplasmosis and has made the unique contribution that positive tests were demonstrated in the aqueous humor but not in the blood serum

of 4 of 10 patients. The labelling of such antibodies with radioactive iodine appears to be a favorable and promising projection for future studies.

In the same laboratory, Dr. Chie Tanaka has been studying the relationship between APC and EKC viruses with hela cell suspensions. Two strains of adenovirus type 8 were isolated from these tissue cultures obtained from typical EKC patients.

Dr. Gunkel is continuing his excellent work in ocular instrumentation and has, this year, developed an apparatus to allow the automatic control of stimulus intensity in recording.

Three projected projects into the coming year show promise. These will be the work on single retinal units by Dr. Michael Fourtes; the work on ultramicroscopic anatomy of the retina by Dr. Theodor Wanko; and the phase microscopy studies by Dr. Aronson and Dr. von Sallmann.

The Epidemiology Branch of the National Institute of Neurological Diseases and Blindness: This Branch under Dr. Kurland has expanded in the past year to include two assistant epidemiologists and more recently in acquiring two geneticists. The addition of a biometrician will complete the initial plans of this unit. Dr. Kurland has continued his studies on amyotrophic lateral sclerosis and other neurological disorders in the Mariana Islands and immigrants of the Chamorro tribe to California. He has arrived at the conclusion that this disorder is hereditary and appears in such large numbers in the Mariana Islands group because of an isolated community being present there with a large amount of inbreeding. Because of the appearance of a disease not unlike amyotrophic lateral sclerosis following gastric resections, Dr. Kurland is studying the cytology of the gastric mucosa in a limited number of admissions at Bethesda. Dr. Kurland's unit projects two new studies in the current year. The first will parallel his Rochester study of neurological disorders in a closed community in which he has now chosen the southern town of Charleston, South Carolina. The second projected study is in the natural history of multiple sclerosis and, in particular, this will utilize veterans of the last war who were admitted with retrobulbar neuritis, and Dr. Kurland plans to follow these individuals with particular interest as to differences in progression between those in southern localities as against northern. Dr. Kurland also did a small study on glaucoma incidence and found before the age of 40 that this disorder is practically

negligible, but by the age of 85 was present in 3% or more of the population. This might indicate that many cases of glaucoma in elderly people are not being adequately diagnosed.

The Branch of Surgical Neurology of the National Institute of Neurological Diseases and Blindness: This branch continues to devote a large amount of its energy in the study of the function of the temporal lobe. 261 operative procedures were done during the past year and of these, 39 included extensive electrical exploration of the cortex and subcortical structures. 24 operations were performed for neoplasia. The majority of patients studied had cerebral seizures. A new system of patient observation has been established on the ward designed for the observation of spontaneous seizures, and a blind control of those with seizures under Metrazol activation in the Electroencephalographic Laboratories has been accomplished. As can be seen in Dr. Baldwin's summary, a particular sequence of events seems to occur in the majority of temporal lobe seizures. He has found the temporal cortex to contain sensory representations for face and jaw. Hypothermia seems to reduce the cortical response to electrical stimulation, and low temperatures reduce the gross volume of arteriovenous malformations but have little effect on intracranial pressures in relation to other brain tumors.

In the Laboratory of Primate Neurology, Dr. Baldwin and Dr. Frost have studied the effects of low temperature on the epileptic discharge in the limbic system and on the electrical activity of the frontal and central cortex. Epileptogenic lesions have been created in the temporal lobes of two chimpanzees and firing has been recorded on the electroencephalogram, and clinical seizures observed. One of the most intriguing of Dr. Baldwin's studies is the correlation of temporal lobe to lysergic acid in normal and abnormal chimpanzees. The psychotic and hallucinogenic effects of lysergic acid do ~~not~~ effect chimpanzees after bifrontal lobectomy or unitemporal lobectomy, but do not after bilateral temporal lobectomy.

Dr. Dekaban has initiated in the past year a much needed large-scale investigation into the abnormalities occurring in the para-natal period. Dr. Dekaban's meticulous study deals with both abnormal and controlled animals and humans. He has thus far collected 31 embryos, as products of abortion, and attempted to demonstrate anatomic deviations and correlate them with the clinical state of the mother during pregnancy. He has collected 43 cases of cerebral abnormalities in the para-natal period and has been able to establish a positive diagnosis in 11, a possible diagnosis in 12, and in 9 was unable to arrive

at the diagnosis. This would indicate that the cause of "cerebral palsy" can be found in at least one-third of the cases if carefully studied. In continuing studies Dr. Dekaban is following all the newborn of two major hospitals in the Washington area and correlating them with the pre-pregnancy history of the mother. In addition, he is running serial sections of mice embryos in 16 progressive developmental stages and of various stages of human embryo as they become available. He finally is attempting to induce central nervous system changes in mice by X-radiation of the pregnant mother.

Dr. Li continues his work in two major areas. First, in the recording from single cells the activity of cortex and muscle. He has found that those cells which give rise to the pyramidal tract receive multi-synaptic responses from the nucleus ventralis lateralis of the thalamus. Such cortical activity is also inhibited by thalamic stimulation. By closed circulation experiments he seems to have demonstrated that the arousal response is not humoral in origin. In his study of muscle, he finds that the muscle fiber is more responsive than the nerve or end plate to cold or temperature. He believes he has demonstrated direct connections of the amygdala to the temporal cortex and that the median ventral nucleus of the hypothalamus inhibits epileptic activity. His second study is an attempt in remote stimulation by radio transmission to excite neurons in the nervous system of higher primates so that such primates may be observed in epileptic seizures without the drawback of cable connections. Dr. Frost is continuing his studies with Dr. Baldwin on memory, personality and perceptual action in temporal lobectomies and has now 84 such cases. In cooperation with Miss Olhoeft he has studied mental retardation under treatment in para-natal disorders and seems to find that although other factors, such as involuntary movements, will be improved the mental retardation does not change under treatment. Dr. Van Buren is continuing his studies on the visual system and the point relationship to the geniculate body and the anatomical relationship of fibers within the temporal lobe. He finds the visual radiation within the temporal lobe to be incongruous with the ipsilateral side showing the most involvement. He finds the macular fibers medially within the temporal lobe. He is continuing his studies of the retina by the Golgi stain, as well as the changes in papilledema. He is continuing his studies on the relief of pain and correlating these with psychological tests and analgesics with the cooperation of Dr. Frost and Dr. Hall.

He has devised a method of insulating instruments against spread of electrocautery discharge. Miss Lewis has continued her efforts in administration of both the animal operating rooms and as chief surgical nurse to Dr. Baldwin. She and Mr. Debroske have devised an operating table which supports two infants simultaneously for the extensive study of a case of craniopagus.

Two new additions to the branch are Dr. Hall and Dr. Klatzo. Their projects hence are projected into the next year. Dr. Hall is studying respiratory balance with a wire frame flow meter in cerebral lesions and is doing much work in hypothermia with Dr. Baldwin. Dr. Klatzo is studying blood brain barrier in cold with particular reference to brain edema and is fluorescince with ultra violet light after injection of fluorescin. Dr. Klatzo also hopes to study muscle proteins by use of antibodies against myosin tagged with fluorescine iocyanate. He is also continuing the study of histopathology of the abnormal epileptogenic tissue that Dr. Alvord started approximately one year ago. In this study he will be joined by Dr. Van Buren. Dr. Klatzo finally will be attempting tissue culture of epileptogenic tissue and will be joined by Dr. Li and Dr. Tower in the electrophysiology and chemistry of such tissue. These are some of the major projects of the Branch of Surgical Neurology.

The Branch of Electroencephalography of the National Institute of Neurological Diseases and Blindness: The Branch, as pointed out initially, has through its activities and reports attracted 4-5 young investigators to it. This branch, of course, is not limited to electroencephalography but does much research in cortical physiology. Because of this, it was felt wise upon the resignation of Dr. Paul Chatfield to transfer the Section of Applied Neurophysiology to this branch and allow Dr. Ajmone-Marsan to pick the new section head of that unit. In addition to its research, this branch, of course, carries out a large service function which takes an equally large amount of the investigators time. Thus, 1,194 inpatients and 277 outpatients had E.E.G.'s during the past year. It speaks highly for the activity of this branch that in spite of this tremendous load, a highly original piece of work on seizure patterns upon metrazol activation acquired such significance as to be published in monograph form. The findings of this project are significant to everyone dealing with seizures in that the interpretations given by Dr. Ajmone-Marsan and his colleagues was such that a high degree of localization of seizure patterns has been

given to bizarre epileptic movements which previously could only be described and were without localizing significance. Dr. Ajmone-Marsan is continuing his close collaboration with the Branch of Surgical Neurology into the deep nuclei of the temporal lobe and particularly with implanted electrodes.

With the utilization of a new drug (6-azauracil) in the Cancer Institute as an antimetabolyte, a new area of interest opened in the physiology of the brain stem in that this drug was able to produce the pattern electrographically of unconsciousness before that stage was reached clinically. Such patients would, however, ultimately become comatose if the drug was continued. Another significant experiment was done with Dr. Ralston and Dr. Ajmone-Marsan in activation of the sites in the brain where spindling occurred by stimulation in certain brain stem structures.

The Section of Clinical Neurophysiology had as its last project the effect of temperature on neuromuscular transmission and this is being completed by Dr. Doudoumopoulos. No new section chief has yet been appointed.

The Branch of Medical Neurology of the National Institute of Neurological Diseases and Blindness: No additions to the Medical Neurology Branch were present during the current year. The neurochemistry laboratory is now one of the biggest sections of the Institute which reflects the logical outgrowth in importance of this particular field. Most of the work in this section has continued in the further elludication of the utilization of glutamine, asparagine, and other derivitives in the formation of glutamic acid and acetylcholine in the brain. New methods have been made to determine levels of asparagine and glutamine in blood and urine; the most useful one at the present time being guinea pig asparaginase. Serum levels reach their height in approximately one hour and fall to normal in approximately 3-4 hours. As the urine level does not rise, it becomes apparent that all asparagine is metabolized. The intermediary metabolism of these amino acids has been studied by utilizing C-14 labelled amino acids. It has been definitely shown that aspartic acid may be metabolized to glutamic acid and glutamine. The isotopically labelled compounds are in the second and fourth carbon group and are not available, therefore, for utilization in decarboxylation in the Krebb cycle. Studies on the clinical

use of asparagine and glutamine show them of limited significance in the percentage pointed out by Dr. Tower and in the summary of the branch. As a result of this, plus experimental data obtained in other units, patients are now being placed on gamma-amino-butyrate and its lactam 2-pyrrolidinone. This, again, necessitated new methods for their detection. In the case of the last named substance, it was found it could be converted to the 2-thio-derivitive in the presence of P_2S_5 and spectrophometrically worked out. This derivitive (2-thio-pyrrolidinone) has been shown to be an analgesic by Dr. Irwin, in the neuropharmacology laboratory, but not asoporific. Dr. Horvath is continuing his studies in the protein of muscle in diseases and normal states and finds a difference in the reaction of actomyosin threads and fibers in myotonia and in normal. Ultracentrifuge studies indicate that the myosin prepared from patients with muscular dystrophy is a polydisperase; that from normal muscle is a monodisperse. Each fraction is characterized by a different sedementation constant. Further studies of gamma globulin in demyelinizing and degenerating diseases of the nervous system are now being undertaken in two laboratories. Dr. Curtis, by use of enzymatic kinetics with L-asparaginase, and in the laboratory of Applied Biophysics, the alpha^2 globulin is being studied by a label of Copper-64. The finding that as little as .1uG. of acetylcholine can be detected by fluorescence in the presence of tetra-phenyl-diboronoxide has given for the first time a method for accurate determination of acetylcholine. The description of the H Disease by Jepsen in England, which occurred familially with cerebellar disturbances, has ellucidated much interest in that a specific indol was found in this disorder.

Dr. Engel and Dr. Tower project into the next year a project along these lines to see if an abnormality of phenylalanine-tyrosine metabolism may be present in other degenerative disorders.

The Section of Neuropharmacology has turned out three excellent manuscripts during the year and are devoting the majority of their efforts to the study of depolarizing and competitive drugs acting upon neurotransmission. By closed circulation technique of the isolated head of a dog, they have found that such agents have no central effect. They find that those neuromuscular blocking agents that provide transmission by depolarization reduce the contraction of directly stimulated muscle. Those compounds which are known to compete with acetylcholine do not influence contraction following direct stimulation. They have indirect evidence that the action of the depolarizing compounds does not arise from spreading of depolarization from the end plate but acts directly on the muscle membrane or upon the contractile unit of muscle. These investigators are doing another closed circulation procedure using an isolated limb and after appropriate manipulation of cholinesterases in the two animals, hope to have a direct comparison of the roles played by the two types of cholinesterase compounds. In the laboratory of Applied Biophysics, with the cooperation of Mr. Robert Bradley and Mr. William Matthews, investigations are underway for localization of cerebral tumors by isotopic detection. The main three isotopes used are Zn-69, I-131, and Arsenic-74. Continual scanning of the head is undertaken and, after suitable amplification, passed through a pulse height analyser. Recording was done by three methods:

1. a mechanical one activated by a scaler
2. a Brown potentiometer
3. by a condenser coupled amplifier through the Brown potentiometer.

The latter system rejects changes of a duration over 15 seconds. Various types of collimation have been used and it has become apparent that none designed so far are good. The unit, therefore, is trying a "sensitive area" collimator with a high density substance (i.e. gold). We are also hoping to increase sensitivity by the use of a new photomultiplier tube which will increase the gain to 10^{16}.

Considerable difficulty has been encountered in the past year in the colored plates for the Atlas of Muscle Disease but it is hoped that this will be published within the next three months. Further work in the histology of muscle will now be histochemical and ultramicroscopic. Three phases are projected: the first is the electromicroscopic changes of diseased muscle, with the cooperation of Dr. Theodor Wanko; second is the utilization of specific fluorescing antibodies to myosin, with the cooperation of Dr. Klatzo; and third is the continuation of the previous work on phase microscopy. Finally, this section will continue the work initiated with Doctors Li, and Wells on the microelectrode recording of single muscle fibers with intracellular glass electrodes. It is expected, in the current year, to apply this technique to man and, in particular, to patients with myasthenia gravis in order to record resting membrane potentials and end plate potentials in diseased states. This is a tedious technique and results should not be expected for at least three years.

This, then, are some of the research projects of the Clinical Investigative Unit of the Institute.

The most apparent trend from this review is that the majority of sections now are directing their energies to productive research, with self-imposed limitations rather than attempting to cover too large and vague a field. The productivity of this method is apparent.

The Institute was helped a great deal by the visiting scientist program, with the aid of two outstanding scientists: Dr. Hans Bornschein and Dr. J. Godwin Greenfield. The former of these helped establish the electroretinography research described above, and the latter aided a great deal in the muscle pathology research.

The research in the wards was aided through the consistent efforts and cooperation of the nursing staff. The Institute this year acquired a new Chief Nurse, Miss Hulburt, and she has shown herself well-equaled to her task. She has been aided by the three head nurses of the ward: Soltow, Pernie, and Malek.

Now that the Institute has reached its full growth, as planned three years ago, no further expansion is anticipated, as noted last year.

With a research unit of this magnitude, certain problems exist and will continue to do so. The most important problem is that of coordination, communication, and loyalty among all members of the institute. There is a tendency, in a unit the size of this, for each individual laboratory to become isolated, and hence defeat the purpose of the Institute. By its very name, an institute should be an integrated attack upon a given problem.

The other problems are relatively minor, with the exception of that of administrative reports. Requests for such reports have probably doubled within the last year, although only four sections were added to the Institute.

The constant dilemma of double responsibility of nursing personnel and administrative officers still offers the temptation to undermine loyalty and distracts from smooth functioning of an integrated unit. In spite of these inherent difficulties, smoothness of these two functions is on the whole efficient, with the exception of Surgical Neurology, in which area there is still incomplete cooperation in operating rooms by the nursing staff.

Four minor, but important, problems have arisen this year with final achievement of staff of the Institute.

First, an institute is by nature concerned with both research and medical care. The more academic an institute becomes, probably the more effective it is in research. However, this may be the time when patient care might suffer. No physician should ever allow patient care to be neglected, or to sub-serve research.

Secondly, is the problem of increasing property. The property records are confused and are labeled ambiguously so that both the investigator and the property man taking the inventory have difficulty in finding the equipment for which the investigator is held responsible.

The final two problems will become of more importance in the near future, but first is the necessity for some type of observation area for epileptic patients, in which one nurse may directly visualize four to eight patients and note the pattern of their seizures.

And the last is the problem of animal space. The clinical investigative unit has, within the Clinical Center, only one double module to furnish all animals, up through CAT, for all the investigative units listed above. This problem is not unique to this Institute, and other areas within the Clinical Center are finding the same difficulties. It is suggested that some type of long-range plan be made to solve the problem of property and animal space.

TABLE 1

TABLE OF ORGANIZATION OF CLINICAL RESEARCH

PERSONNEL

(Personnel on Hand December, 1956)

Office of Clinical Director:

Clinical Director -- Dr. G. Milton Shy, M.D., M.S., M.R.C.P.

Administrative Assistant -- Mr. Elliot Brookman, B.A.

Secretary -- Mrs. Rae Myers

Secretary -- Mrs. Jeanne Layne

Clerk-Stenographer -- Mrs. Theresa Hammond

Branch of Medical Neurology:

Chief -- Dr. G. Milton Shy, M.D., M.S., M.R.C.P.

S.A. Surgeon -- Dr. Glenn A. Drager, M.D., Ph.D.

S.A. Surgeon -- Dr. William K. Engel, M.D.

S.A. Surgeon -- Dr. Gunter R. Haase, M.D.

S.A. Surgeon -- Dr. Caswell K. Smith, M.D.

Medical Officer -- Dr. Tillye Cornman, M.D.

Biologist -- Mr. William Matthews, B.S.

Clerk-Stenographer -- Miss Joyce Jenkins

Clerk-Stenographer -- Miss Dorothy Haase

Section on Biophysical Applications:

Chief -- Dr. G. Milton Shy, M.D., M.S., M.R.C.P.

Physicist -- Mr. Robert Bradley, M.S.

Section on Clinical Neurochemistry:

Neurochemist -- Dr. Donald B. Tower, M.D., Ph.D.

S.A. Surgeon -- Dr. Charles E. Wells, M.D.

Muscle Chemist -- Dr. Beni Horvath, M.D., Ph.D.

Chemist -- Dr. William C. Curtis, Ph.D.

Chemist -- Mr. Milton A. Pogorelskin

Physical Science Aid -- Mr. Edmund L. Peters

Physical Science Aid -- Mr. John W. Phoenix

Physical Science Aid -- Mr. Joseph B. Proctor

Clerk-Stenographer -- Mrs. Virginia Gray

Section on Clinical Applied Pharmacology:

Pharmacologist -- Dr. Richard L. Irwin, Ph.D.

S.A. Surgeon -- Dr. Peter T. Rowley, M.D.

Physiologist -- Mr. Jay Wells

Clerk-Stenographer -- Miss Frances Goldstein

Surgical Neurology Branch:

Neurosurgeon -- Dr. Maitland Baldwin, M.D., M.S., F.R.C.S.

Associate Neurosurgeon -- Dr. John Van Buren, M.D., M.S.C.

Associate Neurosurgeon -- Dr. Choh-luh Li, M.D., M.S.

S.A. Surgeon -- Dr. William M. Headley, M.D.

S.A. Surgeon -- Dr. John F. Lane, M.D.

Sr. Assistant Surgeon -- Dr. Robert G. Long, M.D.

Visiting Scientist -- Dr. Jose H. Mateos, M.D.

Visiting Scientist -- Dr. Peter Gouras, M.D.

Clerk-Stenographer -- Miss Florence E. Beyer

Clerk-Stenographer -- Mrs. Maxine O. Reynolds

Section on Primate Neurology:

Research Assistant -- Miss Shirley Lewis, R.N.

Histopath. Technician -- Mr. Fred Meiller

Staff Nurse -- Miss Karma Eastman

Physical Science Aid -- Mr. Philip McGrath

Medical Aid -- Mr. Andrew Gabor

Physical Science Aid -- Mr. Saxton Howard

Med. Bio. Tech. -- Mr. Allen Rowe

Med. Bio. Tech. -- Mr. Norman E. Mills

Lab. Animal Caretaker -- Mr. Otis Prince

Lab. Animal Caretaker -- Mr. George Duvall

Clerk-Stenographer -- Mrs. Dolores Earley

Clerk-Stenographer -- Miss Vera Douglas

Section on Pain:

Visiting Scientist -- Dr. Kenneth D. Hall, M.D.

Medical Officer -- Dr. Forbes H. Norris, Jr., M.D.

Clerk-Stenographer -- Miss Naomi Bowman

Section on Clinical Psychology:

Psychologist -- Dr. Laurence L. Frost, Ph.D.

Psychologist -- Miss Mildred L. Blevins

Audiologist -- Miss Joyce Olhoeft

Section on Clinical Neuropathology:

Visiting Scientist -- Dr. Igor Klatzo, M.D., M.S.C.

Medical Officer -- Dr. Edward Laskowski, M.D.

Histopath. Technician -- Mr. Daniel Williams

Section on Clinical Neuropathology (Cont.):

Histopath. Technician -- Mrs. Gladys K. Moore

Histopath. Technician -- Mr. Eustace Bourne

Secretary-Stenographer -- Mrs. Arlene Keener

Section on Developmental Neurology:

Visiting Scientist -- Dr. Anatole Dekaban, M.D.

Histopath. Technician -- Miss Marie Kendall

Clerk-Stenographer -- Mrs. Hazel Kisner

Ophthalmology Branch:

Chief -- Dr. Ludwig von Sallmann, M.D.

Surgeon -- Dr. James F. O'Rourke, M.D.

S.A. Surgeon -- Dr. George Goodman, M.D.

S.A. Surgeon -- Dr. Monte G. Holland, M.D.

S.A. Surgeon -- Dr. George R. O'Connor, M.D.

Sr. Assistant Surgeon -- Dr. Samuel B. Aronson, M.D.

Secretary -- Mrs. Frances Dearman

Clerk-Stenographer -- Mrs. Annalee H. Keyes

Clerk-Stenographer -- Mrs. Florence E. Dean

Clerk-Stenographer -- Mrs. J. Ourand

Clerk-Typist -- Mrs. Harriet Murphy

Section on Ophthalmology Pharmacology:

Pharmacologist -- Dr. Frank J. Macri, Ph.D.

Med. Bio. Technician -- Mr. Joseph G. Brown

Section on Ophthalmology Physiology:

Visiting Scientist -- Dr. Michelangelo Fuortes, M.D.

Visiting Scientist -- Dr. Theodo Wanko, M.D.

Section on Ophthalmology Physiology (Cont.):

Physicist -- Dr. Ralph Gunkel, O.D.

Electronic Technician -- Mr. G. Washington

Chemist -- Miss Patricia Grimes

Biologist -- Miss Mary Ann Gavin

Phys. Science Aid -- Mr. Humphrey Patton

Section on Ophthalmology Chemistry:

Chemist -- Dr. Robert A. Resnik, Ph.D.

Chemist -- Miss Ann Roller

Section on Ophthalmology Bacteriology:

Visiting Scientist -- Dr. Chie Tanaka, Ph.D.

Physical Science Aid -- Mr. Lee A. Caldwell

Section on Ophthalmology Histopathology:

Physiologist -- Mr. Leo Caravaggio

Histopath. Technician -- Mrs. Eleanor Collins

Electroencephalagraphy Branch:

Electroencephalagrapher -- Dr. Cosimo Ajmone-Marsan, M.D., Ph.D.

Technician -- Miss Maureen Benson

Technician -- Mrs. Helen Ellerbe

Technician -- Mrs. Carol Hughes

Physical Science Aid -- Mr. Samuel Cooper

Section on Clinical Neurophysiology:

Visiting Scientist -- Dr. Alexander Doudomopoulous, M.D.

Physical Science Aid -- Mr. Jeu Ming

Clerk-Stenographer -- Miss Mary Ziegenfus

Epidemiology Branch:

Epidemiologist -- Dr. Leonard Kurland, M.D., Ph.D.

S.A. Surgeon -- Dr. Milton Alter, M.D.

S.A. Surgeon -- Dr. Samuel Pieper, M.D.

Clerk-- Miss Mary E. Kay

Secretary -- Miss Geraldine McInnes

CLINICAL INVESTIGATIVE UNIT

Publications - 87

	Manuscripts	Books	Total
Medical Neurology Branch	23	4	27
Surgical Neurology Branch	23	0	23
Ophthalmology Branch	22	0	22
Epidemiology Branch	8	0	8
Electroencephalography Branch	8	1	9
	84	5	89

TEACHING

NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

CLINICAL RESEARCH

With the increase in number and type of disorders studied within the clinical unit, it has become apparent that this unit can service a three-year residency program in neurology. Consequently, such forms were placed before the American Medical Association, and the Board of Psychiatry and Neurology, and this unit was examined in the early part of November.

The additional responsibilities of the unit are recognized with such a teaching program. The prime aim of the program as established four years ago, however, still holds. Thus we feel that we should accept at this Institute only clinicians who are going to academic posts and whom, in addition to training as clinical neurologists, we may also give training in research techniques to use in the laboratory of their subsequent position.

Due to the nature of research carried on in the Clinical Investigations Unit of the Institute, the majority of young neurologists, neurosurgeons, and ophthalmologists joining us should have one to two years of training in their specialty before coming to Bethesda. The teaching program for these individuals in the past year has been as follows:

Clinical teaching on each patient admitted

Didactic and laboratory exercises in neuroanatomy, neuro-ophthalmology, neuroradiology, neurophysiology, neuropathology, and biophysics.

In addition, journal clubs have been held at regular intervals. It is our hope by this method to turn out an individual who can apply basic science to clinical problems, and to have an individual also proficient in one or more research techniques that he may utilize in his subsequent academic position.

SERVICES GIVEN BY THE CLINICAL INVESTIGATIONS UNIT of the NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

The services given by this Institute to the Clinical Center of the National Institutes of Health, are as follows:

Seven hundred seventy (770) consultations were rendered in either the inpatient or outpatient areas of other Institutes. Of these, two hundred twenty-nine (229) were Neurological; fifty-two (52), Neurosurgical, and the remainder (489) were Ophthalmological. The electroencephalography laboratory carried out examinations on one thousand, one hundred ninety-four (1,194) inpatients and two hundred seventy-seven (277) outpatients.

Electrocorticographic studies during surgical exploration of the brain was performed on twenty-seven (27) seizure patients, and five (5) patients had extensive studies with implanted electrodes. These figures show an increase of one hundred eighty (180) examinations over the previous calendar year. Approximately eighteen (18) major intracranial operations were done on patients who were admitted to other Institutes. In addition to this, a combined study has been set up with the National Cancer Institute in which a limited number of hypophysectomies are being carried on patients with extensive metastasis from breast cancer.

A total of one thousand, three hundred forty-two (1,342) accessions have now been recorded as being received in the neuropathological laboratories. Chemistry laboratories in the Institute have continued to do spinal fluid proteins.

Continued acceleration for the consulting service of the Institute will increase, until total activation of all the beds of the Clinical Center.

SERVICES GIVEN BY THE CLINICAL INVESTIGATIONS UNIT
(Continued)

Such services, however, are not sterile in that broader interests may be seen by the consulting physician. Problems of mutual interests between the Institutes may also thus be investigated, and have resulted in the publication of three papers in the past year:

1) On the effects of lukemia on the central nervous system

2) On the effects of sickle cell anemia in the retina

3) On the effect of 6-azo-uracil on the electroencephalogram

ANNUAL REPORT *Calendar Year 1956*
OPHTHALMOLOGY BRANCH
NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES AND BLINDNESS

SUMMARY

Outstanding in number and quality were the contributions from the laboratory of Electroretinography. Dr. Bornschein's appointment as visiting scientist to the Ophthalmologic Branch, thus, proved to be of greatest value for the research activities of the entire branch. He, Dr. Goodman, Dr. Iser and Dr. Gunkel were the authors of four published papers and two additional studies have been completed. New basic aspects of the Electroretinogram of the human eye were elucidated in this work and the clinical usefulness of the method with various techniques was systematically explored. Among the studied components of the human Electroretinogram were: wave lengths, intensity and the rate of rise of the photopic stimuli. Results obtained from normal color blind and night blind subjects proved that the "late positivity" was a scotopic B-wave and not a specific photopic red response as claimed by others. Goodman and Iser have studied the scotopic and photopic flicker Electroretinogram. The response of the A, B, and X-waves in this function to changing adaptation and stimulus intensities were shown to be consistent with the behavior of these waves in the single flash electroretinogram. The diagnostic and prognostic value of scotopic and photopic ERG was critically analyzed by Iser and Goodman. The importance of this examination for the differential diagnosis between congenital anamolies or hereditary degenerations and other clinically similar forms of retinal disease was clearly established.

Considerable work has been carried out on the cataract problem in cooperation with Mr. Caravaggio, Miss Grimes and Mrs. Collins. Species differences of radio sensitivity of the lens were found to be of quantitative rather than qualitative nature. (7 species) this provides a basis for extrapolation of experimental data for human radiation cataract which shows cytologically many similarities to senile cataract. In another part of the work morphological studies on the cellular level were compared with biomicroscopic examinations of rats which had been treated with different types of cataractogenic agents. It was concluded that some of these agents produced cataract via injury to the cell nuclei of the germinative zone whereas others attacked primarily the cytoplasm. The prognosis of these experimental cataracts depends, at least in part, on these differences of pathogenetic events. (Two publications in press and one completed to be submitted.)

Studies of the physiology and pathology of the intraocular pressure with emphasis on the central nervous control of this function were continued in the laboratories of physiology and pharmacology with Dr. Macri and Dr. Wanko as co-workers and with the assistance of Miss Grimes. This work encompassed investigations on the dependence of the intraocular pressure changes on blood pressure changes, and of the effect of various pharmacologic agents on centrally elicited eye pressure variations. More recently techniques have been devised (by Dr. Macri) to analyse such effects with respect to the participation of outflow mechanisms and changes of aqueous formation. A notable piece of work deals with innervation of this outflow area--that is the trabecular system in the angle of the anterior chamber. Dr. Holland and co-workers compared the innervation of several species, including man, and obtained important information on these eyes, which might prove to be essential for the understanding of the nervous control of the outflow mechanism. (3 publications).

In a new project Dr. Macri and Dr. Fuortes carried out a remarkable investigation on the effect of several muscle relaxants on the extraocular striate muscles and skeletal muscles. Report of this elaborate experimental approach is pending.

Dr. O'Rourke continued his excellent investigations on tracer methods. The Tripartite approach consisted of 1) studies on the uptake of suitable radioemitters by S-91 mouse melanoma, 2) modifications of equipment for the detection of radioactive tracers in tumors, and 3) defining the limitation in the use of P^{32} and the Geiger tube instrumentation presently used in clinical work. In addition, Dr. O'Rourke initiated the use of gamma sources of zinc and iodine to be employed in Ophthalmology. The observed low uptake of P^{32} by normal ocular tissue, the unfavorable ratio of this uptake between tumor tissue against normal structures, the interference of emissions from the Uvea from those originating in the conjunctiva and extraocular muscles--all these results contribute directly to the clinical problem of tumor localization in Ophthalmology and indicate the need for improvements of the diagnostic tools based on the understanding of underlying principles.

In a clinical study, Dr. O'Rourke and clinical associates are undertaking a systematic evaluation of steroid therapy in patients with uveitis. The number of patients with this disease admitted to the ward should provide the opportunity to collect sufficient observations on the theraputic effects over prolonged periods under better controlled conditions than generally available.

These groups of patients served also in the study of diagnostic procedures particularly in regard to toxoplasmosis as an etiologic factor. In this field, Dr. O'Connor's demonstration of precipitating antibodies in the aqueous humor of the diseased eye by means of the agar-diffusion method represents a valuable piece of work and deserves special mention. In 4 of 10 patients with positive tests the antibodies were demonstrated only on the aqueous humor and not in the blood serum suggesting local formation of antibodies in tissues of the eye. Should this finding be confirmed, the value of Dr. O'Connor's diagnostic procedure would surpass in significance any other test available at the present time.

Dr. O'Connor's work is being carried out in the Microbiological Section. In the same laboratory, Dr. Chie Tanaka continued studies of the trachoma virus, investigated the relationship between APC and EKC viruses and applied the technique of Dr. Huebner to material from patients with uveitis or external diseases. Material from 2 patients suffering from typical epidemic keratoconjunctivitis with punctate Keratitis and pre-auricular adenopathy was suspended in maintenance media and inoculated in Hela cells. Two strains of adenovirus type 8 were isolated from these tissue-cultures obtained from typical EKC patients.

In the Chemistry Section, Dr. Resnik elaborated methods for the fractionation of lens proteins into the homogeneous components. Low temperature alcohol fractionation in conjunction with paper electrophoresis has been adapted with some success. In contrast to the calf and cat lens, the lenses of the rat contain a water insoluble, salt soluble component. Three distinct fractions of the rat lens migrate to the anode and there is a suggestion of a fourth component which moves to the cathode. Studies on the rat lens are of particular interest since experimental cataract and age dependent changes can be observed best in this species. In other studies, Dr. Resnik and Miss Wolff determined the relative amounts of RNA and DNA in the lens. The previous reported studies on the reaction of Alloxan with metals and SH groups was published in the Archives of Biochemistry and Biophysics 64:33-50, September, 1956.

The testing of brightness threshold with the Goldmann-Weekers Adaptometer has the disadvantage that it requires manual operation of the intensity control and recording system. Dr. Gunkel modified this apparatus to allow for automatic control of stimulus intensity and recording and, thus, improved the accuracy and reliability of examinations of dark adaptation. Together with Dr. Bornschein he proved that consistent results were obtainable when the patient's cooperation was

not limited by his illness. Dr. Gunkel's contributions in designing and constructing ophthalmic instruments was of great benefit to the Branch in several areas. He simplified and improved the tangent screen and constructed various types of instruments which serve excellently in experimental work on animals.

The Ophthalmology Branch was most fortunate that two new laboratory units could be set up in the Fall of this year: Dr. Michaelangelo Fuortes as Chief of the Physiology Section, and Dr. Theodor Wanko as Head of the Electronmicroscopy Laboratory joined the staff. It is not the purpose of this report to list the outstanding qualities of these investigators, but it can be said with assurance that their work will greatly add to the research activities of the Branch. Dr. Fuortes will apply cellular microelectrode techniques in studies of the electric activity of retinal elements. Dr. Wanko plans to investigate ultra structures of ocular tissue elements namely, epithelium and fibers of the lens, epithelium of ciliary body and tissue components of the optic nerve.

Finally, it is planned, in cooperation with Dr. Aronson, to subject ocular tissue elements to phase contrast microscopy on material partially obtained by organ tissue techniques. When techniques have been elaborated, work on problems of pharmacodynamics on a cellular level and the influence of deficiency states on cells will follow.

In conclusion, it can be said that most of the projects listed last year have been worked upon and to a great extent reported or published. In the Calendar Year 1956, eighteen (18) papers have appeared in print or were accepted for publication; four (4) additional studies have been completed and will be submitted for publication this year. The number and quality of this contribution does not reflect only on the efforts of the main investigators but also reflects on first-rate technical and secretarial assistance and devotion to this work.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 1 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Ophthalmological Disorders
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Evaluation of Steroid Therapy in Uveitis.
PROJECT TITLE

7. James F. O'Rourke, M.D.
PRINCIPAL INVESTIGATOR

8. Monte G. Holland, M.D.; George Goodman, M.D.; and G. Richard O'Connor, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: (1) By controlled clinical study to assess patterns of uveitis response to steroid therapy with particular emphasis on (a) uveitis activity, and (b) vitreous opacity. (2) To attempt collation of uveitis response patterns observed under combined steroid and chemotherapy regimen with those noted on chemotherapy alone. (3) To elucidate variations in uveitis activity which may result from changes of (a) steroid dosage, or (b) chemical form of steroid.

Methods Employed: Suitably screened patients are admitted to the in-patient service where etiologic surveys are completed. Appropriate chemotherapy, either anti-toxoplasmic or anti-tuberculous, is begun 48 hours before systemic steroid intake commences.

Hormonal therapy is given in the following order of preference: (a) prednisone, oral (b) Hydrocortisone, free alcohol, intravenous (c) ACTH, intravenous, and (c) ACTH, intravenous - alternating with typhoid antigen therapy. Local or subconjunctival administration of steroid is used supportively in most patients.

The responsiveness of uveitis lesions as judged by biomicroscopic, ophthalmoscopic, and visual acuity examinations are recorded and the data abstracted onto a card file with particular emphasis on the features chosen for most intensive study.

Patient Material: Patients are admitted on the basis of having definite uveitis activity with or without vitreous opacity.

Out-patient visits: 269 *

Clinical Project #700. (N-3-701 & N-3-702)

Major Findings: Records suitable for this study have been assembled to date from about 75 cases and preliminary surveys indicate (1) many lestions become responsive to steroid therapy only when the dose is greatly increased; a few respond only to a change of steroid medication. These variations appear unrelated to lesion extent or severity. (2) The responsiveness of uveitis, which is presumed to be toxoplasmic, to specific chemotherapy alone appears, in many cases, equal to that observed on a regimen of combined chemotherapy and steroid intake. Cases complicated by vitreous opacity appear to respond better to the combined therapy. (3) While vitreous opacities are variously influenced by steroid therapy, there have been several encouraging responses observed in the formed as well as in the cellular type, following intensive hormonal therapy.

Significance to the Institute Program: Uveitis as a pathologic process offers the advantage of direct observation of changes which follow or are associated with steroid therapy. A clinical study the control of which clearly exceeds that usually reported and with special emphasis on the features heretofore poorly reported, fills an obvious need.

Proposed Course of the Project: This is a continuing study of the over-all nature of uveitis responsiveness, the current phase of which is outlined above.

Future studies will include (a) further elucidation of the natural history of the disease, (b) the possibly modifying role of stress/adaptation factors, and, (c) the role of thyroid hypo-function and subclinical malnutrition.

*Since patients admitted on this project were also studied on the project entitled, "The Diagnosis and Treatment of Ocular Toxoplasmosis", the number given here reports half the total visits for both projects.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 1 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,000	104,117	$ 114,117	.5	.5	1.

BUDGETED POSITIONS			
PROF	OTHER	TOTAL	PATIENT DAYS
			1186
.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 1 (C)

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

O'Rourke, James F.,M.D.; Iser, Gilbert, M.D.; and Ryan, R.W., M.D. An initial evaluation of Prednisone therapy in ocular inflamation. A. M. A. Arch. of Ophth. 55:323-332, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 2 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Ophthalmology Pharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Study on the Pharmacodynamics of Various Agents Affecting Intraocular Pressure
PROJECT TITLE

7. Ludwig von Sallmann, M.D. and J. Frank Macri, Ph.D.
PRINCIPAL INVESTIGATORS

8. Miss Patricia Grimes
OTHER INVESTIGATOR

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH):

10. PROJECT DESCRIPTION:

Objectives: To test various drugs including the newer ataraxics as well as older compounds for their ability to influence intraocular pressure. It is felt that this approach may provide leads for a more rational medical treatment of patients with glaucoma. The results of this investigation may also shed some light on the mechanisms by which the intraocular pressure is maintained.

Methods Employed: The bilaterality of eye pressure changes influenced by emotions and drug administration as well as normal diurnal variations, point to a neurovascular factor or factors in the regulation of intraocular pressure. Eye pressure is also dependent on changes occurring elsewhere in the body, i.e., heart minute volume, vascular tonus, etc. For these reasons synchronous recordings of variables which have an effect on intraocular pressure, together with eye pressure manometry, offer a new approach to the study of the glaucoma problem on a rational basis.

Multichannel recording with high sensitivity transducers have been developed in the Knapp Laboratory for studies on the intraocular pressure in the last few years. With instrumentation of this type it is possible to compare the effects of drugs on the intraocular pressure of both eyes, the intra-arterial and intra-venous pressure, temperature in the anterior uvea, and the behavior pattern of the pericorneal terminal vasculature, as well as pupils and nictitating membranes. Activity of extraocular striated muscles can be determined electromyographically. The apparatus for such study is now assembled in the laboratory for Pharmacology and Physiology, and work on this problem was initiated twelve months ago with the cat as the experimental animal. It can be said that the present phase of the work confirms the results of previous studies which were limited to eye pressure and blood pressure recordings.

Currently a method is being developed that may permit the simultaneous recording of aqueous outflow. Such a method could serve for the determination of changes in this variable as affected by drugs.

Major Findings: Pharmacological agents, representative of groups of compounds having a different pharmacodynamic activity on the autonomic nervous system, were studied for their effects on the intraocular pressure and subscleral temperature. The results obtained to date indicate that these agents alter the intraocular pressure only insofar as they produce variations of the systemic blood pressure. Thus, the changes of intraocular pressure appear due to changes in intraocular blood volume dependent upon systemic blood pressure responses.

The effect of central stimulation was prevented by Priscoline, Promazine and chlorpromazine. This verifies the sympathetic character of the stimulation.

Changes of formation and outflow of aqeous humor may be superimposed on the described marked effects. In view of the delayed manifestations of such reactions they cannot be demonstrated clearly with the present methods. It appears advisable, therefore, to attempt determinations of aqueous inflow and outflow by the new technical approach.

Patient Material: Patients with various types of glaucoma, admitted on this project, were treated usually with local medications in most instances in combination with systemic administration of Diamox. The eye pressure of these patients was controlled by this means. So far the use of centrally active drugs has not been warranted.

Out-patient visits in 1956: 143.

Clinical Project #711. (N-5-705 & N-5-711)

Proposed Course of the Project: Combination and screening of pharmacological agents in the experimental studies under various conditions with refined technical methods and integration of laboratory data and clinical observations.

Systematic clinical application of results obtained in the experimental study to patients with various forms of glaucoma is forthcoming. The rational use of centrally sedating or tranquilizing drugs in glaucoma patients which do not respond to the usual local treatment appears to be promising, particularly since the autonomic innervation in the outflow area of the eye has been demonstrated in this Branch (reported in project on "Innervation of the Anterior Chamber Angle). Although such therapy is unlikely to be of benefit to all types of glaucoma, it is expected that it will have a place in the medical management of patients suffering from the primary narrow angle type of disease. It is also possible that the outlined approach will be of value in the characterization and differential diagnosis of arbitrarily classified forms of glaucoma.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 2 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
			.5	1.	1.5
FY'57 $10,000	$14,222	$24,222			

BUDGETED POSITIONS			
PROF	OTHER	TOTAL	PATIENT DAYS
			162
FY'57 .5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 2 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

von Sallmann, Ludwig, Macri, F.J., Wanko, T., and Grimes, P. Some mechanisms of centrally induced eye pressure responses. Amer. J. Ophth. 42:130-147, Pt. 2, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 3 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Chemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. A Study of the Proteins of the Lens.
PROJECT TITLE

7. Robert A. Resnik
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATOR(S)

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION: **(N-4-703)**

Objectives: The fractionation of the lens proteins into homogeneous components is the ultimate goal. Any one fraction that is obtained will be used for the determination of molecular weight and in dye binding studies. These data will be used to characterize the proteins from normal and abnormal lenses of various species.

Methods Employed: The ultracentrifuge and electrophoresis will be used to determine homogeneity. Characterization of these proteins by comparison with other proteins will be carried out by the technic of equilibrium dialysis. These methods will be supplemented by any that would be particularly useful as the work progresses.

Major Findings: Initial work using the technic of column chromatography proved to be too time-consuming considering the objectives of this project. The method of low temperature alcohol fractionation, in conjunction with paper electrophoresis, has been adapted with some success to date.

The rat lens appears to contain a water insoluble, salt soluble protein. It is thus essential, when using rat lens, to homogenize the tissue in 0.155 M Sodium Chloride. Calf and cat lens do not contain a

component which has this characteristic solubility. α -crystallin, having a mobility of about 5.5×10^{-5} cm 2/volt-sec., is completely insoluble in 12% alcohol. However, this fraction contains β - crystallin, having a mobility of 1.2×10^{-5} cm^2/volt-sec.

Rat lens contains three distinct components which migrate toward the anode. There is a suggestion of a fourth component which moves toward the cathode. The mobility of this component is greater than -1×10^{-5} cm^2/volt-sec.

The extent to which diffusion and endosmosis might contribute to the appearance of a component moving toward the cathode has not yet been completely resolved. Diffusion in the absence of convection was found to be insignificant.

Significance to the Institute Program: While much data are available on the size, shape, electrostatic, and chemical properties of other proteins, these data are not known for lens proteins. It is possible that some basis to explain changes in the transparency of the lens will be forthcoming from this work.

Proposed Course of the Project: Attempts will be made to obtain results on the cortex and nucleus separately, anticipating that this will facilitate the fractionation.

Once the method has been improved, detailed studies of the properties of these proteins will be started. It is hoped that this information will provide a better understanding of both the aging process and opacification of the lens.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 3 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,000	5,152	13,152	.25	.10	.35

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.25	.10	.35	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 3 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 4 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Chemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Chemistry of Alloxan.
PROJECT TITLE

7. Robert A. Resnik
PRINCIPAL INVESTIGATOR

8. Ann R. Wolff
OTHER INVESTIGATOR (S)

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To study the reaction of alloxan with metals and sulfhydryl groups.

Methods Employed: One means of identifying substances is by comparison of their absorption spectra. The shape of the curve may be used as a qualitative means of identification, while the intensity of the spectrum may be used as a quantitative determination of the substance. In addition, any shift in the wavelength of the absorption maximum is indicative of a reaction taking place. In the case of reactions involving metals, complex formation is said to take place if a ligand (the complexing agent) reacts with a metal. These changes are also detectable by changes in the pH titration curve of the ligand when titrated in the presence and absence of metal.

Major Findings: The reaction of alloxan with glutathione was found to be influenced by the buffer salt used. Although the reaction is pH dependent, the reaction product obtained at pH 6.2, 7.4 in the presence

of phosphate and pH 6.1 in the presence of acetate is identical. However, at pH 7.4 in the presence of bicarbonate and at pH 7.4 in the absence of buffer new reaction products are obtained.

Alloxan reacts with thioglycolic acid to form a substance with an absorption maximum at 315 mu. With the ethyl ester of thioglycolic acid, a compound with an absorption maximum at 340 mu is formed. As a result of these and previous studies, there appears to be a reaction involving both a sulfhydryl and a carbonyl or carboxyl group in the reaction of alloxan with glutathione.

In order of increasing affinity, the association of alloxanic acid with metal cations is copper, cobalt, and zinc.

Significance to the Institute Program: In instances of cataract formation, the free sulfhydryl groups, present in protein and glutathione, are diminished in number. Such changes occur in experimental cataracts induced by alloxan. Although it is true in all probability that the ocular changes that result in diabetes mellitus and in alloxan diabetes are due to the diabetes itself, since the alloxan is known to oxidize sulfhydryl compounds, it is possible that, as a result, it could indirectly deplete the lens of this substance.

Proposed Course of the Project: With these findings, this project is terminated.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 4 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$8,000	5,152	$13,152	.5	1.	1.5

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications

15. NINDB 4 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Resnik, Robert A. and Wolff, Ann. The Reaction of Alloxan with Glutathione and Protein. Arch. Biochem. & Biophys. 64:33. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 5 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology
LABORATORY, BRANCH, OR DEPARTMENT

4. Chemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. A Study of the Nucleic Acids of the Lens.
PROJECT TITLE

7. Robert A. Resnik
PRINCIPAL INVESTIGATOR

8. Ann R. Wolff
OTHER INVESTIGATOR (S)

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH. (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: Heretofore no reports on the relative amounts of ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) in lens have appeared. The qualitative and quantitative aspects of these substances in lens will be studied in lenses from animals of various ages and with lenticular disorders.

Methods Employed: There are many well-established procedures for the spectrophotometric determination of nucleic acids and their components. Thus, analytical procedures for phosphate, sugar, and base will all be used.

Major Findings: The presence of both DNA and RNA in calf lens is indicated by positive orcinol and indole tests. The separation of RNA and DNA from calf lens is in progress.

Significance to the Institute Program: In the course of structural and chemical changes taking place in both normal and abnormal processes, nucleic acids have an important role. In addition to being of importance in growth, nucleotides are able to affect proteins. Sulfhydryl groups appear to be implicated not directly but as a result of the interaction between nucleotides and protein. Changes in the availability of sulfhydryl

groups are related to the changes that take place in cataract formation. Thus, by studying the nucleic acids of the lens both in regard to themselves as well as to their interaction with proteins, it may be possible to get some insight to normal and pathological changes that occur in the lens.

Proposed Course of Project: The concentration of both RNA and DNA in lenses from different species will be determined. In addition, the effect of age and various experimental factors on the nucleic levels will be studied.

Because of the interrelationship between this project and the project on lens proteins, certain phases of both these projects will be closely integrated.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 5 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	#8,000	5,152	#13,152	.25	.50	.75

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.25	.50	.75	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 5 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 6 (C)
SERIAL NUMBER

2. NINDB 3. Ophthalmology Branch
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Bacteriology 5.
SECTION OR SERVICE LOCATION (If other than Bethesda)

6. The Diagnosis and Treatment of Ocular Toxoplasmosis
PROJECT TITLE

7. G. Richard O'Connor, M.D.
PRINCIPAL INVESTIGATOR

8. James F. O'Rourke, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

Dr. Leon Jacobs of the National Institute of Allergic and Infectious Diseases, Laboratory of Tropical Diseases, is engaged in a parallel research project. His aim is to detect specifically labelled Toxoplasma antibodies in the eyes of infected rabbits, using the azo-dye, Echt Säure Blau, as a labelling agent. Dr. Jacobs is carrying on parallel work in the chemotherapy of Toxoplasmosis in infected mice.

This project complements animal experimentation carried out by Doctor Don Eyles at the Memphis Public Health Service Facility.

Parallel studies on the treatment of human systemic toxoplasmosis are being carried out on the wards of the National Institute of Allergic and Infectious Diseases under the direction of Dr. Norman B. McCullough.

10. PROJECT DESCRIPTION

Objectives: To find more specific methods for the diagnosis of ocular toxoplasmosis. To determine through scrutiny of the patients' medical history and serological evidence the various factors of etiologic significance in

the acquisition of the disease. To observe the course of the ocular disease and its response to various forms of therapy.

Methods: (a) The Agar-Diffusion Method

Samples of various body fluids such as aqueous humor, blood serum, gamma globulin extracts of blood serum, or spinal fluid, are allowed to diffuse through buffered semi-solid agar toward a source of Toxoplasma antigen derived from the peritoneal exudate of infected mice. If precipitating antibody to Toxoplasma is present in the fluid tested, a visible line of precipitate will be formed in the agar at a given point, where the relative proportions of diffusing antibodies and antigen molecules are optional.

If precipitins are found in the aqueous humor (obtained by paracentesis of the anterior chamber of the eye) an attempt is made to correlate this finding with the precipitins in the blood serum of the patient. In every case where the volume of the sample permits, the Toxoplasma Dye Test is also performed on both blood and aqueous humor at the same time.

Semi-quantitative estimates of the amount of precipitating antibody present can be made by 1) serial dilution of the antibody-containing fluid to an end-point where precipitation is just barely visible, and 2) measuring the distance from the antibody source at which maximal precipitation occurs. All other factors being equal, the concentration of antibody at any point is taken to be inversely proportional to the square of its distance from the antibody source.

(b) The Detection of Labelled Toxoplasma Antibody in the Uveal Tract of the Eye

Fractions of gamma globulin from the sera of patients or rabbits containing known high levels of dye-test antibodies and anti-Toxoplasma precipitins are prepared by either electrophoretic separation or by ammonium sulfate precipitation. These fractions are labelled with radio-active sodium iodide (I^{131}) in the presence of elemental iodine and potassium iodide. Unbound radio-active iodide is removed by allowing the mixture to filter through an anionic resin exchange column. The labelled antibody, so produced, is tested both for precipitin activity and radio-activity. An agar plate is set up as in section "a" and if a precipitin line is formed, the latter is tested for radio-activity by means of a direct contact radio-autograph of the agar surface.

The proposed method will include the intra-ocular or intra-venous inoculation of such labelled antibody into

rabbits with previously established Toxoplasmic infections of the retina of one eye. If antigen is naturally liberated in the lesion, it is hoped that the labelled antibody will become sessile at such sites, where it can be detected by external counting, by radio-autography of tissue sections, or by Geiger Counter analysis of emulsified tissue.

Patient Material: Granulomatous uveitis cases are obtained by physician referral. Screening for the presence of high Toxoplasma Dye Test titers or toxoplasmin skin reactions can be done before the selection of the patient. Those patients with a high degree of inflammatory reaction in the anterior part of the eye are of particular interest for aqueous study.

Clinical Project 701. Number of out-patient visits is 269. (N-3-701)

Major Findings: Precipitating antibodies to Toxoplasma have been found in a large number of sera tested, and in the gamma globulin fractions of these sera, as well. The precipitating antibody, originally thought to be a simple homogeneous system giving rise to a single precipitin line is now known to be a composite of at least four substances, not all of which are present in every serum. The visualization of four precipitin bands has been made possible through further refinements of technique such as the concentration and purification of antigen from mouse peritoneal exudate.

A total of 33 specimens of aqueous humor has been examined by the agar-diffusion technique. Most of these were obtained by paracentesis of the eyes of in-patients, but a few specimens were sent by mail from other clinics or private physicians. Ten of these specimens were positive for precipitating antibodies. In four patients precipitating antibodies were found in the aqueous humor but not in the blood serum of the patient. This has tended to support the idea that there is local formation of antibody in the eye; for in these cases it cannot be argued that precipitins have gained access to the eye from the blood stream due to increased permeability of the blood-aqueous barrier.

Although a positive Toxoplasma Dye Test has been found in every specimen of aqueous humor containing precipitins, there seems to be no good correlation between the Toxoplasma Dye Test titer and the amount of precipitating antibody present. The strongest precipitin reaction in aqueous was obtained from a patient with an aqueous dye-test titer of only 1:4; whereas another patient with an aqueous dye test of 1:256 gave a barely perceptible precipitin reaction. Conversely patients with serum dye test titers as high as 1:4096 have shown no precipitins in this fluid.

It may well be that the precipitating antibody and the dye-test antibody are two different substances, elaborated independently during different phases of the disease.

The precipitating antibody has been labelled satisfactorily with I^{131} without apparent loss of antibody activity. The labelled globulin produces not only a visible precipitin line in agar, but that line can also be shown to be radioactive. This has been proven largely through radio-autographs, using emulsion-covered microscope slides in direct contact with the agar.

Significance to the Program of the Institute: The precipitin technique holds promise of providing a specific diagnosis of ocular Toxoplasmosis, particularly if it can be shown that the antibody is elaborated within the eye itself.

The agar-diffusion technique also offers the possibility of testing a single small quantity of aqueous against multiple antigens simultaneously. As such, it may have general usefulness in the etiologic evaluation granulomatous uveitis, the diagnosis of which has always been vague and speculative.

The labelled antibody similarly offers a new approach to the diagnosis of lesions in situ, provided that accurate localization of the antibody in the tissue can be achieved.

The results of treatment of in-patients with suspected ocular Toxoplasmosis, using Pyrimethamine and the Sulfa drugs (alone or in combination with steroids) suggests that these patients may be benefited by drug therapy, particularly in the early, exudative stages of their disease. It is therefore of obvious value to make an early specific diagnosis, when possible.

Proposed Course of Project: To continue the testing of aqueous humor using refined and purified antigens. To establish, if possible, the role of precipitating antibody in the particular phase of the disease in which it is elaborated. To investigate by simultaneous protein analysis of serum and aqueous, the probability that precipitating antibody to Toxoplasma is formed within the eye itself. To compile a large series of data on the relative amounts of dye test antibody and precipitating antibody in the same samples, and thus determine the relation of the two entities to each other. To precede with the radio-active labelling of highly concentrated globulin solutions for injection purposes, and to test the predilection of such labelled antibody for lesions in the uveal tract.

We will continue to observe and treat patients with presumed toxoplasmic uveitis, with special emphasis on information to be gained from 1) paracentesis and examination of the aqueous humor, 2) response to drug therapy, and 3) from eventual detection of toxoplasmic lesions in situ.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 6 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,000	$104,117	$114,117	/		/

BUDGETED POSITIONS			
	PROF	OTHER	TOTAL
FY'57	/		/

PATIENT DAYS - 1186

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S): Dr. Leon Jacobs of the National Institute of Allergy and Infectous Diseases, is carrying on animal experiments as well as tissue culture, serological, and epidemiological studies on Toxoplasma gondii, in cooperation with our branch. He furnishs facilities and supervision for the Toxoplasma Dye Test on both serum and aqueous humor. He has attempted to culture Toxoplasma from the aqueous humor and from emulsified eye tissue specimens by animal inoculation of these materials.

Animal experiments involving induced Toxoplasma infections in the posterior pole of the eye are performed in Dr. Jacob's laboratory, using animals supplied by NIAID.

Samples of mouse peritoneal exudate, used as sources of antigen, as well as high-titer immune rabbit sera are supplied by Dr. Jacob's laboratory.

The Clinical Research Division of the Eli Lilly Company, Indianapolis, Indiana, has also supplied us with samples of antigen for investigative purpòses. It is likely that they will supply us with large amounts of antigen, harvested from infected check embryos, in the coming year.

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 6 (C)

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

O'Connor, G. Richard. Anti-Toxoplasma precipitins in aqueous humor; A new application of the agar-diffusion technique. A. M. A. Archives of Ophthalmology 56:5, October, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 7 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Microbiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA

6. Study of Viruses Affecting the Eye.
PROJECT TITLE

7. Chie Tanaka, M.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATOR (S)

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

This project parallels similar investigations carried out under the direction of Dr. Robert J. Huebner, National Institute of Allergy and Infectious Diseases. Dr. Ruebner's group is performing neutralization tests and complement fixation tests with Adenovirus type 8. Similar methods of virus isolation and cultivation are undertaken by this laboratory, using explants of tissue obtained from patients.

10. PROJECT DESCRIPTION:

Objectives: 1) To study the cultivation of trachoma virus. 2) To study the relationship between pharyngoconjunctival fever and epidemic keratoconjunctivitis. 3) To culture viruses from cases of uveitis of unknown etiology.

Methods Employed: This project is concerned with the cultivation of the viruses of trachoma, epidemic keratoconjunctivitis and unknown viruses suspected of causing uveitis in tissue culture. The technique includes explantation of conjunctival tissue and iris tissue, as well as direct inoculation of aqueous humor and of scraping material from patients into several different tissues; i.e., Hela cells, Chang's strain of conjunctival epithelium cells, monkey kidney cells and amnion cells.

Examination of infected tissue cells by electronmicroscopy is planned.

After isolation of the viruses, methods of identification are pursued as follows:

1. Serological reaction of the isolated viruses with the sera of trachoma, EKC, and uveitis patients.

2. Study of the biologic properties of the viruses: their stability, their resistance to antibiotics, their filterability, their pathogenicity for laboratory animals, and their production of soluble toxin.

3. Reproduction of experimental virus diseases in laboratory animals, i.e., monkey or apes and rabbits.

Patient Material: Tissue samples from active trachoma patients with numerous inclusions and active cases of epidemic keratoconjunctivitis are preserved by lyophilizing or by suspending scraping material in maintenance media. They are sent by air from Dr. Yukihiko Mitsui, Kumamoto, Japan.

Iris tissues or aqueous humor samples from active uveitis cases are obtained from patients on the Ophthalmology wards at NIH.

Out-patient visits: 5.

Clinical Project #714. (N-3-709)

Major Findings: Two strains of adenovirus type 8 were isolated in Hela cells from typical EKC patients. These patients showed the classical punctate keratitis and preauricular adenopathy associated with EKC disease. Scraping material from the conjunctivae of these patients was suspended in maintenance media and inoculated into Hela cells.

Significance to the Institute Program: Trachoma is still the eye disease of greatest worldwide distribution and importance. Temporary control can be obtained with antibiotics and improvements in sanitary conditions. Cultivation of the trachoma virus becomes an urgent demand and will aid in ultimate control of the disease. The trachoma committee of WHO is interested in promoting studies in this area.

The effect of virus culture studies on uveitis might be of very great significance since a definite etiological diagnosis can rarely be made in present day studies of uveitis. If virus culture were positive, much of the guess-work in current diagnosis might be eliminated by a laboratory test.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 7 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
			1.	1.	2.
FY'57 $15,000	5,152	$20,152			

BUDGETED POSITIONS			
PROF	OTHER	TOTAL	PATIENT DAYS
			213
FY'57 1.	1.	2.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Specimens of immune serum, viral antigens and tissue culture cells have at various times been obtained from Dr. Huebner's laboratory (NIAID). In addition, various tests such as the complement fixation reaction have been carried out by his group on material being studied by the Ophthalmology Branch.

Advice and assistance in several other phases of tissue culture have been obtained from various branches of NIAID.

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 7 (C)

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Tanaka, Chie. Epidemic keratoconjunctivitis in Japan and the Orient. Am. J. Ophth. (in press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Invited to participate in symposium on viral keratoconjunctivitis, San Francisco, California, September 7 and 8, 1956.

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 8 (C)
SERIAL NUMBER

2. NINDB 3. Ophthalmology Branch
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Ophthalmology Physiology 5. _____
SECTION OR SERVICE LOCATION

6. Studies on Central Nervous System Control of Intraocular Pressure
PROJECT TITLE

7. Ludwig von Sallmann, M.D. and J. Frank Macri, Ph.D.
PRINCIPAL INVESTIGATOR(S)

8. Theodor Wanko, M.D. and Miss Patricia Grimes
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: In previous and now published work of this group it has been shown, that electric stimulation of the hypothalamus and adjacent areas in the anesthetized cat can elicit changes in the IOP (intraocular pressure) which either reflect blood pressure elevations and falls or appear independent of the responses in general circulation. Such central nervous influences upon the IOP deserve consideration both in regard to the regulation of the IOP under normal conditions and to the mediation of glaucomatous attacks. The dependance of such experimentally induced IOP-changes on general blood pressure variations and/or on contraction of striate or smooth extraocular muscles were studied for possible extrapolation of the experimental data for the human situation. Analysis of the mechanisms of the induced IOP-changes centered in this study on the relationship of BP and IOP responses.

Additional information on the possible central nervous control of the IOP is expected from stimulation experiments

on decerebrated preparations and subthreshold stimuli which could be applied for a prolonged period of time. Under these experimental conditions the determination of outflow and formation of aqueous humor may render insight in the finer mechanics of the effects. Preliminary exploration of cortical influences on the IOP has been initiated. Also under consideration is the picking up of evoked potentials induced by increasing the IOP.

Methods Employed: Up to the present the cat served as the experimental animal in all experiments. Stimulation of various areas of the brain is performed by means of a Horsley-Clarke stereotaxic apparatus, square wave stimuli delivered by a Grass S-4 stimulator, and biphasic stimuli according to the technique recently described by J. C. Lilly. The IOP changes are recorded by means of either Statham transducers or Sanborn Electromanometers. Intraocular blood volume changes are studied by the use of a thermocouple inserted in the subscleral space anteriorly or by means of P-32 labelled red cells and measurement of the change in radio-activity. Electromyogram analysis will be extended and muscle tension studies will be made when effects are noted which could possibly be ascribed to striate muscle activity. Methods are also being developed which would aid in the determination of outflow and formation of aqueous humor, so that such measurements can be made during periods of brain stimulation. Moreover, stimulation of the cortex is being performed by hand-placed ball electrodes. Attempts to pick up "evoked potentials" will be continued with appropriate needle electrodes and recorded from oscilloscopic tracings.

Major Findings: Results obtained to date by stimulation of various areas of the posterior hypothalamus and the medial ventral thalamus or intraocular pressure indicate the following: the rise of intraocular pressure is accompanied by a rise of subscleral temperature; the rise is not mediated through the cervical sympathetic nerve; it is not due to mechanical pressure exerted by the striated extraocular muscles; occlusion of the common carotid artery during continuous stimulation causes first a transient fall of intraocular pressure in the homolateral eye, followed by a sustained rise to the pre-occlusion level. Subscleral temperature changes in these cases follow a pattern similar to the intraocular pressure responses. Measurements of Beta particle emission in the anterior segment of the eye after IV injection of P-32 labelled red cells do not provide information with respect to submaximal changes of intraocular blood volume. The effect of the intraocular pressure rise could be abolished by Priscoline and Thorazine. To date, only a few experiments have been performed in regard to effects of stimulation of the brain stem and the cortex on the IOP so that no comment can

be made at this time. An attempt to pick up "evoked potentials" in the ventral hypothalamus as a result of increasing the IOP has met with no success in three experiments.

Significance: These studies present the first attempt to investigate by systematic experiments the part played by the central nervous system in the regulation of the intraocular pressure. Interpretation of the results with reference to the IOP pathology of the human eye requires further experimentation.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 8 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
			.5	1.	1.5
FY'57 $10,000	5,152	$15,152			

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 .5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 8 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

von Sallmann, L.; Macri, F.J.; Wanko, T.; and Grimes, P. Some Mechanisms of Centrally Induced Eye Pressure Responses. Amer. J. Ophth. 42:130-147, Pt. 2, 1956.

von Sallmann, L. Central Control of Intraocular Pressure. Glaucoma Trans. of First Conf., Dec. 5, 6, and 7, 1955. The Josiah Macy, Jr. Foundation. published November 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 9 (C)
SERIAL NUMBER

2. NINDB 3. Ophthalmology Branch
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Ophthalmology Physiology 5. _____
SECTION OR SERVICE LOCATION

6. Detection of Ocular Tumor by Isotope Methods
PROJECT TITLE

7. James F. O'Rourke, M.D.
PRINCIPAL INVESTIGATOR

8. Robert Bradley, B.S. and Humphrey Patton, B.S.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To develop more accurate tracer methods for diagnosis of intraocular and intraorbital malignancys by these three methods of investigation: (1) Basic animal tumor studies - determination of uptake of suitable gamma and beta emitting labelled compounds by the S-91 mouse melanoma. (2) Physical: evaluation and modification of equipment for detection of tumor radioemissions. (3) Clinical - study by P-32 uptake procedures of patients who are tumor suspects to (a) assess critically the P-32 and Geiger tube modality as presently used and (b) to attempt clinical studies using gamma emitting isotopes of zinc and iodine.

Methods: (1) Basic - Tissue assay of S-91 mouse melanoma continues following recent completion of studies on the Differential Absorption Ratio (tumor) of P-32 and Zinc 69. The tumor DAR is calculated following tissue assay by the wet ash method and these results are collated with similar data from liver, eyes and whole body at intervals of one and twenty-four hours.

(2) Physical - Modifications of the collimated spectometer

system of Francis and Bell have been undertaken by the medical neurological branch, using the 3" scintillation counter recently assembled here. Pending completion of alterations in the design of this device studies of ocular and orbital problems have been deferred.

(3) Clinical - Radiophosphorus uptake studies continue to be made on suitable material derived from patients screened from the following diagnostic categories: (a) retinal detachment, solid or serous; (b) unilateral exophthalmos; (c) progressive or non-responsive lesions of the lid and lacrimal apparatus; (d) cysts and tumors of the iris; (e) blind phthisical eyes; and (f) retinoblastoma suspects. External and retrobulbar Geiger counting are done on suitable patients whenever possible, usually 24 hours after radiophosphorus injection. When available, ocular and tumor tissue have been assayed postoperatively for P-32 content again by wet ash methods used in basic studies. Contemplated examination of patient material using the collimator scintillation probe have not yet begun.

Major findings: Studies to date indicate (1) in general a low uptake of radiophosphorus by normal human and animal ocular tissue: Human tumor uptake appears to exceed that of normal ocular tissue by only a factor of 10: (2) S-91 mouse melanoma takes up zinc 69 in amounts which are significantly in excess of those found using P-32, (3) the microcuries per milligram uptake of conjunctiva and extraocular muscle following systemic injection of P-32 exceeds that of ocular tissue in the rabbit during the first 24 hours.

Patient Material: Clinical Project No. 707. There were 70 out-patient visits. (N-12-707)

Significance to the Institute Program: The continued modification of tumor localizing equipment should improve the resolution of such devices for tumor detection in both CNS and eye and ultimately bring ocular and optical malignancys within the range of equipment sensitivity. (2) Clinical studies of normal ocular disease by the use of labelled anti-body will depend, in its clinical phase, on the availability of appropriately precise counting and recording devices.

Proposed course of project: (1) Basic studies: there exists a need for measurement of Differential Absorption Ratio of I^{131} in malignant melanoma; such will be done using S-91 mouse tumor, (2) scanning studies of mouse tumor; and, later, of suitable clinical malignancies will be undertaken when modifications of the collimated spectometer system are complete. (3) Attempts will be made to localize malignant melanoma of the choroid using a larger and more sensitive

type Geiger-Mueller tube which is collimated so as to increase resolutions while preserving adequate counting rates.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 9 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,000	5,152	$15,152	.5	.5	1.

BUDGETED POSITIONS			
PROF	OTHER	TOTAL	PATIENT DAYS
			70

FY'57

.5	.5	1.

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 9 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

O'Rourke, James F.; Bradley, Robert; and Patton, Humphrey. Fundamental Limitations of Radiophosphorus Counting Methods Used for Detection of Intraocular Neoplasm. A.M.A. Arch. of Ophth. (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NI[illegible] 10 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Effects of Muscle Relaxants on IOP* and Extraocular Striate Muscles.
PROJECT TITLE

7. Frank J. Macri, Ph.D. and M.G.F. Fuortes, M.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: During the past year, several reports have been published indicating that muscle relaxants similar to decamethonium produce a rise in IOP. This action has been preliminarily ascribed as a contractile effect on the extraocular striate muscle. Since these compounds are used in clinical practice, their application to the eye from both a pharmacological and physiological basis becomes of considerable interest. It is proposed to study the action of these agents in greater detail as well as to study the action of similarly acting compounds.

Methods Employed: Anesthetized or decerebrate cats are used in all experiments. Facilities for the simultaneous recording of IOP, muscle tension, and electromyograms are currently available to us. The inferior oblique muscle was selected for study because of ready accessibility of both muscle and motor nerve. Bipolar wire electrodes are used for electromyograms. A Grass strain gauge connected to a carrier pre-amplifier measures muscle tension changes with sufficient accuracy for our purposes. Muscle tension changes, together with the EMG's, are recorded by a movie camera from oscilloscopic tracings. By means of a proper diode, resistor and condensor, the electrical responses of the muscle can be integrated as to frequency and magnitude and recorded on a four-channel stylus recorder.

* Intraocular Pressure

The muscle tension is also traced on this instrument, together with IOP and BP. Thus, one can determine the time sequences of the events that occur as well as the changes in these variables.

Major Findings: Exploratory experiments in this laboratory have verified the contractile effects of decamethonium-like compounds on the extraocular striate muscle. Preliminary data indicate that both decamethonium and succinylcholine induce contraction of these muscles, which is, with smaller doses, a tetanic contraction, and with larger doses a contracture. Tensilon, a drug which has a brief but beneficial effect in patients with myasthenia gravis has been found, in this study, to also induce an elevation of the IOP together with an increase of the electrical activity in the extraocular striate muscle.

Significance to the Program of the Institute: (1) To serve as a guide for the clinical use of these agents in ophthalmology. (2) To increase our knowledge of the pharmacology of these agents. (3) To add in the understanding of the physiology of the extraocular striate muscle.

Proposed Course of the Project: To continue the investigation with particular reference to structure-activity relationships in the eye muscle and to compare this relationship with that prevalent in other striate muscle systems.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 10 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,000	5,152	$15,152	.5	1.	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 10 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 11 (C)
SERIAL NUMBER

2. NINDB 3. Ophthalmology Physiology
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology 5.
SECTION OR SERVICE LOCATION (If Other Than Bethesda)

6. Electro-physiology of the Retina
PROJECT TITLE

7. M. G. F. Fuortes, M.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: In recent years, it has become possible to record electrical activity from single cells of the central nervous system by means of intracellular micro-electrodes. These studies have yielded interesting results concerning the physical properties of nerve cells and the basic mechanisms of their excitation. It is thought that the techniques developed in the mentioned studies on the electrical activity of cells in the central nervous system may now be applied to analysis of the functions of retinal elements. If suitable optical instrumentation can be devised, it is possible that penetration of retinal elements may be performed under direct visual control.

Methods Employed: Glass micropipettes are drawn to a tip diameter of less than 1/2 micron and are then filled with a salt solution. They then form a small electrode having a resistance of about 100 mega ohm. These pipettes are then attached to a micromanipulator and are connected, through a suitable input stage, to an amplifier. The retina of a cold-blooded animal, dissected out from the eye, is immersed in Ringer fluid or mineral oil. A high-power dissecting microscope is used to watch both the retina and the microelectrode.

It is hoped that it will thus be possible to insert the micropipette into previously identified retinal elements and to lead off from these the electrical changes correlated to their activity.

Major Findings: The techniques mentioned above are at present under development, and no findings have been obtained so far.

Significance to the Program of the Institute: If it should prove possible to record the changes occurring during activity in all types of retinal cells, one could reconstruct the events intervening between application of visual stimuli and excitation of ganglion cells and optic nerve fibres. If instead, activity can be led off only from certain types of cells, some of these events should be induced. In either case, the proposed research may further our understanding of the events occurring in the retina during normal vision and thus provide a basis for better interpretation of pathological events.

Proposed Course of the Project: The course of this project will be conditioned to a large extent by the facilities which will become available in the near future. The basic instruments required for this research have been ordered between July and August, 1956, but have not yet arrived. Once the basic instrumentation is available and the first successful experiments have been performed, further refinements of technique and instrumentation may prove necessary. It can be reasonably anticipated that a period of perhaps six months will have to elapse before any concrete results are obtained.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 11 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$31,000	$5,152	$40,152	1.	1.	2.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1.	1.	2.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 11 (C)
SERIAL NUMBER

16. *LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:*

17. *LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:*

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 12 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Design and Construction of Ophthalmic Instruments.
PROJECT TITLE

7. Ralph D. Gunkel, O.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. IF IN N.I.H.)

10. PROJECT DESCRIPTION:

Objectives: To make improvements in the instruments used in ophthalmic examination, treatment, or related laboratory work.

Major Findings:

(1) The tangent screen illuminator has been simplified and improved in both utility and appearance. Without resorting to a shutter arrangement, it now provides 7-foot candles at 1 meter with the switch down, and 7-foot candles at 2 meters with the switch up. A shaped face-shield has been added, which occludes one eye while limiting the view of the seeing eye to the immediate area of the screen. The shield eliminates the need for the eye patch, which is both inconvenient and unsanitary. The examiner is still able to observe the eye being tested.

(2) Automatic intensity control and continuous recording systems have been added to the Goldmann-Weekers Adaptometer. They are further described in another report.

(3) Contact lens electrodes, various kinds of specula, and other devices for animal work have been designed and constructed as the need arose.

Significance to the Institute Program: The tangent screen illuminator has been favorably received by most of the clinical associates, so has been placed in both eye clinics for routine use.

The improvements to the Goldmann-Weekers Adaptometer developed enough interest to warrant a separate project, which is also being reported.

It is not possible to evaluate the small devices and appliances made for other investigators, but it is believed that they are appreciated.

Proposed Course of Project: It seems desirable that this project continue along its present lines, with sufficient flexibility to allow for collaboration in any part of the branch, and the development of relevant, fruitful ideas from whatever source.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 12 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,000	5,152	$9,152	.5		.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5		.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 12 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Gunkel, Ralph D., and Ryan, Ralph W. A Self-Recording Remote-Control Tangent Screen. American Journal of Ophthalmology, 40: 897, 1955.

Gunkel, Ralph D. An Improved Tangent Screen. Transactions, American Academy of Ophthalmology and Otolaryngology, May-June, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 13 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Automatic Intensity Control in Testing Dark Adaptation.
PROJECT TITLE

7. Ralph D. Gunkel, O.D.
PRINCIPAL INVESTIGATOR

8. Hans Bornschein, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To simplify and standardize the procedure for testing brightness thresholds and recording the series which comprise the dark adaptation curve.

Methods Employed: Since the Goldmann-Weekers Adaptometer seems to be the most practical and commonly used instrument for clinical purposes, it was considered suitable for this work. The main drawbacks to the instrument relate to the fact that it depends upon manual operation of both the intensity control and the recording device. Variations in the rate of change of the intensity and in the lag of recording both introduce definite and unpredictable errors in the results. Also, the procedure requires the continuous attention of a reasonably skilled operator.

Replacement of the original recording device (punch-type stylus) by an inkwriter has given satisfactory, continuous recording. Installation of a 1 RPM Bodine motor with suitable reduction gears and safety devices has provided a constant rate of change of intensity of 1.5 log units per minute. The only manipulation necessary is done by the subject in raising a switch lever when he fails to see the flashing test light and lowering the switch lever as soon as he sees the light.

Patient Material: Subjects for the reported series were selected from Clinical Center patients and staff so as to include both normal and pathological dark adaptation curves.

Major Findings: Consistent and repeatable results were obtained in recording both normal and pathological dark adaptation curves except in a few cases where the patient's cooperation was limited by his illness.

Significance to the Institute Program: The automatic method improves the standards of accuracy and reliability in the determination of dark adaptation curves, while at the same time reducing to a minimum the supervision required of the examiner.

Continuous recording of the dark adaptation curve presents greater detail than has been previously available, and facilitates analysis of the rod-cone break and other events of the cycle.

Good dark adaptation curves have been helpful in analyzing and evaluating electroretinographic data for both clinical and basic studies. In most cases, they provide corroborative evidence, and one test will almost predict the findings of the other.

Proposed Course of Project: It is expected that use of the modified Godmann-Weekers Adaptometer will be retained as standard procedure for both clinical and laboratory work.

A further modification of the adaptometer is in process which will permit threshold determinations in different areas of the retina, thereby obtaining a "threshold field". It will undoubtedly bear some relation to the standard visual field, but its usefulness is difficult to predict.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 13 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,000	5,152	$10,152	.5		.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5		.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 13 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Gunkel, Ralph D., and Bornschein, Hans. Automatic Intensity Control in Testing Dark Adaptation. A.M.A. Archives of Ophthalmology. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 14 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION
3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE
5.
LOCATION (If other than Bethesda)

6. Electron Microscope Studies on the Epithelium of the Lens, the Ciliary Body and the Optic Nerve
PROJECT TITLE

7. Theodor Wanko, M.D.
PRINCIPAL INVESTIGATOR

8. Ludwig von Sallmann, and Mary Ann Gavin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION: (N-4-703)

Objectives: Investigations of ultrastructures of ocular tissue elements in a tripartite study comprising, first, epithelial cells and fibers of the lens; second, cells of the two layers of the ciliary epithelium; and third, tissue components of the optic nerve. Some of these structures have been subjected to electron microscopic analysis in a few laboratories in the past years, but information contained in the published reports appears to be of preliminary nature and limited in scope.

Methods Employed: An RCA Electron Microscope, Model EMU-3, will be used in these studies. Control and comparative examination will be carried out with the aid of phase contrast and light microscopy.

The lens of the rat is selected for the first part of the work, in view of the considerable body of information pertaining to experimentally induced lens pathology in this species. Fixation methods presently used for this tissue

require re-evaluation. After dehydration the specimens will be embedded in methacrylate to be sectioned on a Servall Porter-Blum microtome.

The ciliary process of the albino rabbit will be the source of material in the second study. Fixation with osmiumtetroxide or other compounds containing OsO_4 will preceed the embedding procedure.

The optic nerve of the rat will be employed in the preliminary work in the third part of the study. The use of osmiumtetroxide is planned for initial fixation in vivo of the exposed structures with the animal under general anesthesia and fixation will be continued after removal of the material.

Major Findings: None. It is planned to begin the development of the fixation and embedding procedures within four weeks. Electron microscope studies will follow as soon as the equipment of the laboratory is assembled.

Significance: The various areas of the lens epithelium which differ biologically and physiologically from each other have not as yet been the subject of investigations of their ultrastructures. Information obtained may reveal basic morphologic differences between the germinative and the resting part of the epithelium and prove to be of importance for the understanding of age -- dependent and induced pathologic changes of the various zones of this cell layer.

The classification of the epithelium of the ciliary processes as secretory sensu strictiori or merely as participating in the active transfer mechanism of the barrier has been the topic of extensive controversy for many years. Studies on ultrastructures of these cells may give a lead to the function of the epithelium and the role it plays in the formation of aqueous humor.

The work on the normal optic nerve may provide a basis for the study of pathologic events.

Proposed Course: The outlined studies on the selected normal tissue material should open the way for investigation of other species and pathological changes of these tissues.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 14 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	#48,000	5,152	#53,152	1	1	2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 14 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 15 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA

6. Physiologic studies of the human electroretinogram in response to intermittent light stimuli.
PROJECT TITLE

7. George Goodman, M.D.
PRINCIPAL INVESTIGATOR

8. Gilbert Iser, M.D.
OTHER INVESTIGATOR

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: The human electroretinogram has been studied in response to individual light stimuli (single flash electroretinogram) and intermittent light stimuli (flicker electroretinogram).

Analysis of the single flash electroretinogram has demonstrated that the positive potential elicited from the human eye may be differentiated into a rapid photopic wave (x-wave) and a slower scotopic wave (b-wave). The preceding negative potential (a-wave) can also reflect photopic and scotopic processes. However, no systematic approach to the behavior of a-, b-, and x-waves in the human flicker electroretinogram, under different conditions of adaptation and stimulation, has been reported.

The purpose of this study is to investigate the photopic and scotopic components of the human flicker electroretinogram in different states of adaptation, while changing stimulus intensity and frequency, in a total color blind, a congenital night blind, and normal subjects.

Methods Employed: A contact lens electrode led the electroretinographic potentials from the subject's anesthetized cornea to an eight-channel direct writing EEG machine. A gas discharge lamp was used which produced brief flashes of light of fixed duration at frequencies varying from one to eighty per second. Neutral and colored filters were utilized to vary the intensity and wavelength of the light stimulus.

Patient Material: Five subjects with normal eye findings were studied with flicker electroretinography. They were obtained from the in-patient and out-patient services of the Ophthalmology Branch. (N-10-710)

Three patients with congenital retinal anomalies were studied with flicker electroretinography. They were referred to the Ophthalmology Branch specifically for these studies.

Major Findings: The scotopic ("rod system") flicker electroretinogram was studied in normal and totally color blind subjects. The flickering positive potentials (b-waves) decreased in amplitude with increasing rates of stimulation and/or stimulus intensity. A maximum flicker fusion frequency of 22/sec., was obtained with light stimuli of moderate intensity, which decreased with stimuli of higher intensity. These effects were due to the influence of light adaptation, produced by the repetitive light stimuli, on the scotopic apparatus.

The photopic ("cone system") flicker electroretinogram was studied in normal and congenitally night blind subjects. The complex response patterns were interpreted in terms of the interference of the negative (a-wave) and positive (x-wave) components of the single flash photopic electroretinogram. Flicker fusion frequency increased with each increment in stimulus intensity, in a range from about 28/sec. to 70/sec.

Under conditions where both photopic and scotopic components were present (mixed flicker electroretinogram), the behavior of these components proceeded independently, as demonstrated in the isolated photopic and scotopic flicker electroretinogram. The flicker fusion frequency-light intensity curve showed two branches, which was a composite of the curves obtained in the totally color blind and congenitally night blind subjects.

The response of the a-, b-, and x-waves in the flicker electroretinogram to changing adaptation and stimulus intensity, were consistent with the behavior of these waves in previous studies of the single flash electroretinogram.

Significance to Institute Program: The implications of these investigations in human electroretinography are of importance to the student of retinal physiology, and to the growing number of ophthalmologists who use electroretinography as an objective test of retinal function. In particular, these studies have served as the theoretical basis for the development of new diagnostic techniques in clinical electroretinography which are now under investigation in the Physiology Section.

Proposed Course of the Project: The previous studies were confined to only one stage of dark adaptation, in addition to testing in the light-adapted state. Further attention will now be directed to the scotopic flicker electroretinogram and the response obtained during different stages of dark adaptation, while changing intensity and frequency of stimulus.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 15 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
			1.		1.
FY'57 $9,000	$5,152	$14,152			

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 1.		1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications

15. NINDB 15 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Goodman, George and Iser, Gilbert. Physiologic studies with flicker electroretinography. Am. J. Ophthalmology 42:212-26, (October, Part II), 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 16 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Quantitative Studies of the Human Electroretinogram in response to Single Light Stimuli.
PROJECT TITLE

7. Hans Bornschein, M.D.
PRINCIPAL INVESTIGATOR

8. George Goodman, M.D.* and Ralph D. Gunkel, O.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: The human electroretinogram elicited by a single light flash is a complex pattern of negative and positive potentials. The analysis of these different components is of fundamental importance, since their origin and significance are still controversial, and their behavior in response to different stimulus factors is unsettled.

The studies undertaken in this investigation include the effect of wavelength, intensity, rate of rise of the light stimulus, and changing states of adaptation, on the amplitude and temporal course of different waves in the human electroretinogram. Wherever possible, subjects with congenital night blindness and total color blindness are compared with normal controls. The selective lack of scotopic and photopic function in these anomalies results in the absence of specific electroretinographic components. This simplifies the complex pattern of response, allows a more detailed investigation of remaining components, and aids in the analysis of their photopic or scotopic origin.

* Principal investigator for proposed projects.

Methods Employed: A contact lens electrode led the electroretinographic potentials from the subject's anesthetized cornea to a double beam cathode ray oscilloscope with appropriate preamplifiers. Photographic records of the response were made by means of a kymograph camera. A gas discharge lamp was used which produced brief flashes of light of fixed duration. Neutral and colored filters were utilized to vary the intensity and wavelength of the light stimulus.

Patient Material: Subjects with normal eye findings for physiologic studies were obtained from the clinical in-patient and out-patient services of the Ophthalmology Branch, or were referred to the Ophthalmology Branch for study by other Institutes. Number of patients studied: 10. (N-10-713)

The patients with congenital retinal anomalies were referred to the Ophthalmology Branch specifically for electroretinographic studies. Number of patients studied: 4.

Major Findings:

Study #1: The relationship between the implicit time and amplitude of the human scotopic b-wave was studied while varying the wavelength and intensity of the light stimulus. It was found that the implicit time of the b-wave varied between 60 and 140 milliseconds as a simple exponential function of the amplitude. Furthermore, the influence of colored light stimuli on the implicit time of the b-wave was related to stimulus intensity, and not to a specific effect of wavelength.

The results obtained from normal, color blind, and night blind subjects proved that the "late positivity" interpreted by other investigators as a specific photopic red response was actually the scotopic b-wave.

Study #2: A congenitally night blind, totally color blind, and three normal subjects were studied electroretinographically with single flash stimuli under identical conditions. The effect of increasing stimulus intensity and dark adaptation on the negative electroretinographic wave (a-wave) and positive wave (b-wave and/or x-wave) was investigated in each subject.

The negative and positive waves (a-wave and b-wave) of the total color blind reflected exclusively scotopic activity, and the positive wave (x-wave) of the congenital night blind reflected photopic activity. However, the negative wave (a-wave) of the night blind subject demonstrated both photopic and scotopic activity as in the normal subject.

The intensity curve of the positive response in the normal subject showed a second increase in amplitude after reaching a plateau, which has not been previously described. Comparison to the intensity curve in the subject with retinal anomalies suggests that this is due to the addition of the x-wave to the positive response.

Study #3: The human electroretinogram was elicited from five normal subjects, a total color blind, and a congenital night blind, with special attention to high speed recording of the early negative wave (a-wave). The results suggested that the "break" splitting the a-wave into two portions (a_1 and a_2) is caused by a positive hump leading a series of later humps, rather than two a-waves of different latencies. This interpretation of the split appearance of the a-wave does not interfere with the assumption of its dual character (i.e. photopic and scotopic) nor with the possible difference in the temporal course of the two components.

Significance to the Institute Program: These investigations in human electroretinography are of importance to the retinal physiologist, and to the growing number of ophthalmologists who use electroretinography as a diagnostic clinical procedure. Specifically, these studies have aided in the interpretation of the clinical electroretinogram, and in the correlation of the objective data obtained from the electroretinogram with the results of psychophysical studies of vision also under investigation in the Physiology Section. Both objective and subjective methods have been used together in studies of patients referred to the Ophthalmology Branch with retinal disease.

Proposed Course of the Project: Intensive studies of patients with retinal anomalies will continue, with special emphasis on the correlation of electroretinographic findings with the data obtained from psychophysical tests of dark adaptation and light thresholds. Further studies will include the investigation of vitamin A lack on the human electroretinogram, in conjunction with detailed psychophysical studies.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 16 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 16 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Bornschein, Hans, Goodman, George, and Gunkel, Ralph D. Temporal aspects of the human electroretinogram. Arch. Ophth. (in press)

Bornschein, Hans and Goodman, George. Comparative electroretinographic studies in congenital night blindness and total color blindness. (completed)

Bornschein, Hans and Goodman, George. Studies of the a-wave in the human electreretinogram. (completed)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 17 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA

6. Evaluation of electroretinography as a useful clinical tool.
PROJECT TITLE

7. Gilbert Iser, M.D.
PRINCIPAL INVESTIGATOR

8. George Goodman, M.D.*
OTHER INVESTIGATOR

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: Electroretinography is the study of the electrical potentials elicited from the retina by a light stimulus. It affords the ophthalmologist an objective test of retinal function.

During the past ten years, clinical electroretinographic studies have concentrated mainly on the scotopic portion of the electroretinogram or b-wave. This consists of the potential evoked in the dark-adapted eye by a light stimulus of moderate intensity. The scotopic electroretinogram has been found to have definite limitations as a diagnostic aid, especially in diseases involving the macula specifically, or cone (photopic) system in general.

Although the photopic component of the electroretinogram was first described in 1945, its analysis has not as yet become part of routine clinical electroretinography. The present study was therefore undertaken to determine whether the photopic electroretinogram, as elicited by single flash and flicker (intermittent stimuli) techniques would provide more diagnostic information than the standard single flash scotopic electroretinogram in retinal disease.

* Principal investigator for proposed projects.

Methods Employed: Patients are tested while resting in bed. The light source is a gas discharge lamp (Grass Photic Stimulator) which allows for variation of intensity and frequency of the light flashes. Colored filters were used to change the spectral composition of the light. The potentials are picked up simultaneously from both eyes with contact lens electrodes, and the binocular recordings are made on a Grass eight-channel direct writing EEG machine.

After preliminary experimentation, four measurements were selected for routine study:

1. The photopic single flash or x-wave: This is the positive component of the response of the light-adapted eye to a stimulus of high intensity.

2. Photopic flicker--amplitude at 30/sec.: Photopic flicker is defined as the response of the light-adapted retina to high intensity flickering stimuli. The amplitude of the flicker waves at a frequency of 30/sec. is measured as an index of photopic function.

3. Photopic flicker fusion frequency: In this study, the flicker fusion frequency is defined as the frequency at which the retina is observed to respond to less than half of the high intensity flicker stimuli.

4. The scotopic single flash or b-wave: This is the positive component of the response of the dark-adapted eye to a light stimulus of low intensity.

Patient Material: Patients suitable for study are drawn from those referred to the Ophthalmology Branch for investigation. In many cases, they have been referred specifically for the purpose of clinical electroretinographic study. Patients with normal eye findings are used as controls, and those with retinal detachment, hereditary, inflammatory and vascular retinopathies are studied for diagnostic changes. Approximately 75 patients were studied electroretinographically during the past year, with 111 out-patients visits involved. Clinical Project #710. (N-10-710)

Major Findings: The study of both the photopic and scotopic electroretinogram has its greatest diagnostic and prognostic value in conditions which selectively involve either the photopic or scotopic mechanism. It appears to be particularly valuable in the investigation of cases with congenital anomalies, as well as cases with hereditary degenerations. In other types of retinal disease (for example, retinal detachment and chorioretinitis) where such selective involvement is not found, and in lesions involving the macula alone, the photopic recording was found to be no more informative than the scotopic. In addition, studies with red light stimuli show no significant variation from white stimuli in lesions of the central retinal area.

The retinal response to high intensity flicker light is a valuable method of recording photopic response, and has some advantages over the single flash x-wave. However, it appears that the study of the amplitude of the flicker wave itself at a frequency of 30/sec. is more reliable than attempting to measure the point of fusion.

Photopic flicker recording is a useful adjunct to the standard scotopic single flash technique in clinical electroretinography.

Significance to the Institute Program: New techniques in clinical electroretinographic testing were developed which have been valuable in the diagnostic study of patients referred to the Ophthalmology Branch with retinal disease. They have also helped to establish more firmly the usefulness of electroretinography as a diagnostic procedure in clinical ophthalmology.

Proposed Course of Project: The scotopic and photopic electroretinogram will continue to be studied in patients referred to the Ophthalmology Branch with retinal disease. In those cases where a dissociation between scotopic and photopic responses is noted, the electrical responses will be compared to estimates of photopic and scotopic function obtained by intensive psychophysical studies (i.e., perimetric dark adaptation, light thresholds, and flicker fusion frequency). Wherever possible, attempts will be made to extend both the electroretinographic and psychophysical studies to the families of these patients.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Date

11. NINDB 17 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,000	$8,600	$17,600	1.		1.

BUDGETED POSITIONS			
	PROF	OTHER	TOTAL
FY'57	1.		1.

PATIENT DAYS
98

13. BUDGET ACTIVITY:

RESEARCH	☐	ADMINISTRATION	☐
REVIEW & APPROVAL	☒	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 17 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Iser, Gilbert and Goodman, George. Clinical studies with flicker electroretinography. Am. J. Ophth. 42:227 (October, Part II), 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 18 (c)
SERIAL NUMBER

2. NINDB 3. Ophthalmology Branch
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Physiology 5.
SECTION OR SERVICE LOCATION (If other than Bethesda)

6. The Effect of Rate of Rise of Photic Stimuli on the Human Electroretinogram.
PROJECT TITLE

7. Hans Bornschein, M.D.
PRINCIPAL INVESTIGATOR

8. Ralph D. Gunkel, O.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objective: To study the qualitative and quantitative changes in the components of the human ERG produced by varying the rate at which the light stimulus reaches its full intensity.

Methods Employed: Light stimuli from a 15-watt fluorescent tube are timed by means of a modified pendulum shutter and attenuated by various filters. The ERG is picked up by a Burian Allen contact lens electrode from the anesthetized cornea. After suitable amplification the ERG and the light stimulus are observed on a double-beam oscilloscope. Photographic records are made with a kymograph camera.

Patient Material: Patients exhibiting a low level of baseline activity are selected by trial from among the available normal controls and patients with other than eye disease. Clinical Project 713. (N-10-713)

Major Findings: It has been found that the a-wave can be eliminated from the electroretinogram with a slowly rising

stimuli. The characteristic change in the b-wave is a prolongation of the response, without marked decrease in amplitude.

Significance to Institute Program: The data obtained in this project contributes materially to the present knowledge regarding the factors affecting the form of the human electroretinogram.

Proposed Course of Project: This project could well be extended to cover slower rates of rise than have hitherto been investigated, but it would require a different type of shutter mechanism, and an amplifier with longer time constant.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 18 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 18 (C)
SERIAL NUMBER

16. *LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:*

Bornschein, H. and Gunkel, R.D. The Effect of Rate of Rise of Photic Stimuli on the Human Electroretinogram. Amer. Journ. Ophth. 42:239-243 (Oct) 1956

17. *LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:*

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 19 (C)
SERIAL NUMBER

2. NINDB 3. Ophthalmology Branch
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Histopathology 5.
SECTION OR SERVICE LOCATION (If other than Bethesda)

6. Studies on Diet and Drug Induced Experimental Cataract
PROJECT TITLE

7. Ludwig von Sallmann, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Leo Caravaggio, M.S.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: This project was initiated to obtain a broader basis for the understanding of the processes of lens opacification of different nature. Most of the studied experimental lesions have their correlates in human lens pathology and therefore may have applicability to the human situation. In the past experimental cataracts have been studied and compared with respect to their biomicroscopic appearance or a gun barrel view was obtained by subjecting a limited number of preparations of one kind of cataract to histopathologic examination. In the present study a rather wide survey of lenticular opacities of various origin was obtained and the site of the primary lesion established. The cataractogenic agents employed comprised a radio mimetic drug, myleran (1,4-dimethanesulfonoxybutane), galactose feeding, alloxan injection and tryptophane deficiency state.

Major Findings: Galactose. Galactose and Alloxan produced similar biomicroscopic changes consisting of excessive vacuolization of the young fibers in the equator of the lens. This stage is preceded by excessive increase of mitosis in the epithelium and moderate degeneration of

cell nuclei of the epithelium. Here as well as in tryptophane deficiency cataract, fiber changes appear before extansive damage to the epithelial cells are noticed. The early increase of cell division might indicate the activation of a defense mechanism rather than a lesion which leads to fiber damage.

Tryptophane Deficiency. No signs of lens epithelium damage was encountered at the time when fiber changes became visible on clinical inspection. In contrast to these observations myleran feeding produced first degenerative lesions in the germinative zone and of the nuclei in the lens bow with migration of the damaged cells. Similar to cataract produced by ionizing radiation, the fiber changes appear to be the result of the injury to the cell nuclei in the germinative zone.

Technique: See project on Effects of Ionizing Radiation on the Lens of Various Species of Experimental Animals.

Significance: The comparison of biomicroscopic, cytological and histological changes observed at various time intervals after the introduction of the cataractogenic agent or the deficiencies and the recovery after their withdrawal give us insight into the sequence of morphological events leading to cataract, and should add to the knowledge of the pathogenesis of various types of cataract in man.

Proposed Course: As any approach to the cataract problem on a purely morphological basis is by nature incomplete, studies of such material by histochemical and biochemical methods in cooperation with Dr. Resnik is contemplated. In addition it will be sought to employ phase contrast studies on cell material of such lenses, and, in corporation with Dr. Wanko, electron microscopic studies are planned.

Clinical Project No. 712. Forty out-patient visits.
(N-10-712)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 19 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,000	5,152	$18,152	.5	1.5	2.

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.5	1.5	2.	258

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Columbia University, College of Physicians and Surgeons, - on a technical level. (sectioning of eye globes).

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 19 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

von Sallmann, L. The Lens Epithelium in the Pathogenesis of Cataract. Trans. Amer. Acad. Ophth. & Otol. (in press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

13th Jackson Memorial Lecture at American Academy of Ophthalmology and Otolaryngology, by Dr. L. von Sallmann, October, 1956.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 20 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Ophthalmology Histopathology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Study on the Innervation of the Anterior Chamber Angle.
PROJECT TITLE

7. Monte G. Holland, M.D.
PRINCIPAL INVESTIGATOR

8. Ludwig von Sallmann, M.D. and Mrs. Eleanor Collins
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION: **(N-5-711)**

Objectives: There is a considerable amount of evidence that a neurovascular mechanism is operative in the eliciting of glaucomatous attacks and contributing to factors which regulate the inflow and outflow of the aqueous humor. It is well established that the angle of the anterior chamber, and in particular, the trabecular meshwork, Schlemm's canal, and collector channels is the anatomical locus of the outflow of aqueous humor from the eye. In view of the importance of the trabeculum in regulating the outflow of the aqueous humor and thus in participation in the control of intraocular pressure, it is the purpose of the present project to systematically investigate the innervation of the trabeculum, Schlemm's canal, and outlet channels in several vertebrate eyes. Attempts will also be made to determine the genre or types of fibers represented in the neural population of this region. This study, then, is in line with the work on central nervous influences on the intraocular pressure, since it deals with the search for receptors and effectors for nervous stimuli.

Methods Employed: The methods used are the silver-staining techniques, particularly the Gros-Schultze modification of Bielschowsky's stain, and newer silver impregnating methods which will be compared with the results obtained with methylene blue vital staining. By

sectioning the trabeculum in various planes, it is anticipated that silver impregnation and methylene blue staining will selectively demonstrate the nerves and permit a close study of the anatomy and morphology of the nerve endings in the trabeculum and outlet channels.

The studies are being carried out on human, monkey, bird, and rabbit eyes.

In the second phase of this study, which is concerned with the determination of the origin or kind of the nerve fibers represented in the trabecular region, the superior cervical sympathetic, ciliary, and Gasserian ganglia are being extirpated in rabbits and the course of the resulting degenerating nerve fibers are studied by the use of methylene blue vital staining and the silver method of Nauta.

Major Findings: The major effort thus far has been concentrated on the study of the normal neurohistology of the angle of human, monkey, chicken, and rabbit eyes. The innervation of the angle in these eyes was shown to consist of a plexiform arrangement of delicate arborizing axons which terminated as free axonal filaments in the trabeculum and adjacent to Schlemm's canal and collector channels. An important finding was that no specialized receptors or "neural end organs" were present in the region of the angle in the eyes examined.

Present activity is concerned with the generic classification of the nerve fibers in the trabeculum. Preliminary results to date, based on degeneration experiments, indicate that both sympathetic and parasympathetic fibers are present in the neural population of this region, the latter appearing in noticeably larger numbers. Future work will be concerned with determining whether or not somatic afferent nerve fibers are also present.

Significance to Institute Program: If the innervation of the components of the trabeculum can be established on morphological grounds it will offer a new piece of evidence indicating how nervous impulses may be mediated in regulating the intraocular pressure. It would be of fundamental importance in particular with reference to the neurovascular mechanisms involved in regulating the intraocular pressure and also have significance in reference to the glaucoma problem. Evidence has steadily accumulated indicating that the trabeculum, Schlemm's canal and collector channels are extremely important in the regulation of the normal intraocular pressure and also the probable site of resistance to aqueous outflow in glaucoma. Through the systematic study of the innervation of these structures, it is hoped that a morphological basis will be found to complement the understanding of the basic physiology of the outflow mechanism.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 20 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57 $14,000	5,152	$19,152	1	1	2

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 1	1	2	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications

15. NINDB 20 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Holland, Monte G., von Sallmann, Ludwig, and Collins, Eleanor, M. A study of the innervation of the chamber angle. Am. J. Ophth. 42:148, No. 4, Part II, October, 1956

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 21 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology Branch
LABORATORY, BRANCH, OR DEPARTMENT

4. Histopathology
SECTION OR SERVICE

5.
LOCATION (If other than Bethesda)

6. Study of Submicroscopic Structures of Lens and Corneal Cells by Phase Contrast Microscopy.
PROJECT TITLE

7. Ludwig von Sallmann, M.D.; Samuel Aronson, M.D.
PRINCIPAL INVESTIGATOR(S)

8. Leo Caravaggio, M.S.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION: (N-4-712)

Objective: Studies of Ocular tissue elements by phase contrast techniques have been carried out during the past five years by several investigators, but the technical approaches selected by them provoke doubt as to the correctness of interpretation, since obvious artefacts in the published photomicrographs are considerable in extent and number. Thus it seemed advisable to apply newer techniques for gaining information on submicroscopic structures of ocular cell elements obtained from in vivo material as well as from organ culture techniques. With the results of investigations on normal cellular material as the basis, the effect of various physical and chemical noxae and the prevention of such effects could be initiated. The purpose of this study, then, is first the broadening of our knowledge of fine cell structures and, second, of induction and interception of injurious effects on a cellular level. Work on the problems of pharmacodynamics and the influence of deficiency states on cells also fall under this project.

Methods Employed: Tissue culture techniques will primarily be carried out on newborn rat and rabbit tissues; on human tissue whenever available. Primary explants of corneal and lens epithelia will be transferred to coverslips and cultures in roller tubes. Transplants from these cultures will be studied in depression slides and perfusion chambers by phase microscopic techniques. Photographic methods will embody photomicrographs and time-lapse cinephotomicrography.

Organ culture techniques will be carried out on similar tissues. Depression slides, watch glasses, and perfusion chambers will be employed as culture chambers. Primary explants will be placed directly in these chambers.

The Rose perfusion chamber will be employed in the study of pharmacologic and toxic effects on the above-mentioned cells. Time-lapse cine-photomicrography will record continuous intra-cellular changes.

Major Findings: Since the investigators on this project are now in the process of setting up the technical equipment, no findings are as yet available.

Significance to Institute Program: At present the information on ocular cytology of the eye and the effect of injurious agents, situations and pharmacologically active compounds on cells are based mainly on the examination of fixed and stained material. It can be expected that insight into physiological and pathological process and prevention of the latter can be deepened and ocular therapy may benefit from this work.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 21 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,000	5,152	$15,152	.5	1.	1.5

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 21 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 22 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Ophthalmology
LABORATORY, BRANCH, OR DEPARTMENT

4. Ophthalmology Histopathology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Effects of Ionizing Radiations on the Lens of Various Species.
PROJECT TITLE

7. Ludwig von Sallmann, M.D. and Leo Caravaggio, M.S.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: The effects of an isodose of X-ray was compared on 7 species for more than a year. Since data on the pathogenesis of radiation cataract in the human lens cannot be obtained in early stages in which the sequence of events have significance, information based on the many species allows for extrapolation of the data for the human. It has been shown in previous studies that age changes and those produced by ionizing radiation exhibit great similarities. To prove this point further, about 40 human lenses, both clear and cataractous, were examined after the Feulgen Reaction to clarify the role which the lens epithelium might play in the development of these cataracts.

Methods Employed: The technique of quantitation of the mitotic activity in radiation induced cell degeneration on whole mounts of the lens epithelium was employed on about 600 eyes with the second non-irradiated lens serving as control. Comparisons were made between the cell population in various species, at various age groups, and in from 10 to 12 time intervals after exposure of one eye to 1,000 r x-rays. These data were compared with the results of histological examination of celloidin imbedded lenses in which the migration of epithelial cells and the fiber changes could be observed. Moreover, they were correlated to the in vivo observations on mice, rats, guinea pigs, rabbits, cats, dogs and Rhesus monkeys.

Major Findings: The lens epithelium of normal eyes of adult animals contain dividing cells in ratios per hundred thousand cells varying from 101 (mouse) to 4.2 (dogs) and 2.9 (monkeys). The number of dividing cells in the epithelium of very young rabbits, cats and dogs are multiples of those found in adults. Extrusion of chromatin is a common finding in the lens epithelium of normal kittens and puppies, but was not observed in very young rabbits.

Exposure to the X-ray beam induced depression or complete inhibition of mitosis which was short-lasting and partial in mice and rats but continued close to zero levels for about one week in dogs, cats and monkeys. This phenomenon was followed in all species by an overcompensating increase of cell division. The increment reached the highest peaks in dogs and cats.

Radiation induced cell degeneration with nuclear fragmentation was extensive in mice, rats and rabbits; it was surpassed strikingly by a burst of extruded chromatin globules in dogs and cats. The distribution of these particles between normal regularly arranged epithelial cells suggests restoration of a disturbed nucleus cytoplasm relationship rather than a lethal injury to the nucleus in the dog and cat lens epithelium.

The onset of biomicroscopically visible lens opacities was delayed in dogs and monkeys as compared to other species. This fact and the characteristics and magnitude of cell proliferation and fiber lesions indicate a quantitative difference between dogs and monkeys and other species in the damage produced in the lens by the same dose of X-rays. However, the lens of all animals responded qualitatively in the same manner to the radiation injury.

The examination of human eyes provided evidence of the high incidence of proliferation of cells from the germinative zone backward and the degeneration of such cells which seem to give rise to the cataractous fiber damage. Such proliferation of the equatorial cells in the direction to the posterior pole occured also in clear lenses of the aged and can be considered as an earlier stage of pathology which precedes the development of opacities. In contrast to these observations in the germinative zone, changes of the surface epithelium anteriorly do not contribute greatly to the process of cataractogenesis.

Significance to the Program of the Institute: The combined studies on various species and the observations on the human normal and cataractous lens contributes to a better understanding of pathogenesis of cataract formation in general.

Patient Material: The patients admitted under this project are listed in project on "Studies on Diet and Drug Induced Experimental Cataract (Clinical Project #712). In view of the similarity in the cytopathology of radiation induced and senile cataract, the observations of x-ray, cataract have definite bearing on the problems of cataratogenesis in old age and vice versa.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 22 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
			.5	1.5	2.
FY'57					
$13,400	5,152	$18,552			

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.5	1.5	2.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications. 15. NINDB 22 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

von Sallmann, Ludwig, Caravaggio, L., Munoz, C.M. and Drungis, A. Species differences in the radiosensitiveity of the lens. Amer. Journ. Ophthal. (in press)

von Sallmann, L. The Lens Epithelium in the Pathogenesis of Cataract. Trans. Amer. Acad. Ophth. and Otol. (in press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

13th Jackson Memorial Lecture at American Academy of Ophthalmology and Otolaryngology, by Dr. von Sallmann, October, 1956.

ANNUAL REPORT Calendar Year 1956
EPIDEMIOLOGY BRANCH ACTIVITIES
NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES
AND BLINDNESS

SUMMARY

A basic activity of the Epidemiology Branch is the collection, tabulation and analysis of statistical data on the frequency and distribution of disorders of the nervous system. A "pilot" study carried on in Rochester, Minnesota in 1954-1955 continues to provide data on neurological disorders which are of sufficient interest to call for several individual reports. The latest of these are on glaucoma and cerebral palsy. The report on the methods and results of the survey for other disorders, although not yet ready for publication, provides the basis for epidemiologic surveys, of selected chronic neurologic and ophthalmologic disorders, which are being conducted in cooperation with the Medical College of South Carolina. Plans for similar surveys at other medical centers are proceeding and it is expected that a study of the relative frequency of these disorders for Charleston County, South Carolina and Halifax, Nova Scotia will be under way early next year. An analysis of mortality statistics for the U.S., Canada in particular, and other countries for some disorders, is under way and is expected to complement the pilot study report.

The epidemiologic investigation of amyotrophic lateral sclerosis in the Mariana Islands led to genetic investigations of this disorder in the U.S. and other countries. Evidence obtained in the Mariana Islands and among Chamorros who migrated to California indicated that a hereditary form of amyotrophic lateral sclerosis probably existed among these people. Hereditary amyotrophic lateral sclerosis has been noted or observed in at least 36 pedigrees of twelve different nationalities since this study began. A recent explanation has been offered for all classical amyotrophic lateral sclerosis, most cases in the world apparently being "sporadic". This is based on the similarity of amyotrophic lateral sclerosis mortality rates in all countries studied (nine to date) other than Guam and the other isolated Mariana Islands. It has been hypothesized that a fixed

spontaneous mutation rate in conjunction with one overall average "penetrance" results in a consistent annual amyotrophic lateral sclerosis mortality rate for these large populations. The isolation and small population of Guam, at a time when the disease was introduced (about 1700) there, plus "genetic drift" or some selective survival factor is believed to account for the extremely high incidence on this island at present.

Further epidemiologic and genetic studies of amyotrophic lateral sclerosis are planned in Guam and on Saipan. In the latter area, comparisons of prevalence among the Chamorros and Carolinians are contemplated. Among the Chamorros, intensive surveys are planned to determine the age and sex distribution as accurately as possible. Therapeutic studies on Guam have provided negative results; further tests will be made as new compounds are developed or offered for test.

A study of the incidence of congenital anomalies among the Chamorros is now under way on Guam. Several unusual finger and ear anomalies were noted among children in U.S. families in which amyotrophic lateral sclerosis trait was observed. It is our impression that serious congenital anomalies are prevalent among the Chamorros; whether this is so, and if so, is limited to families with the amyotrophic lateral sclerosis trait is to be determined.

Because of our interest in the amyotrophic lateral sclerosis problem and the belief that a metabolic defect, perhaps due to some abnormality in the upper gastro-intestinal tract predisposed patients to amyotrophic lateral sclerosis, a cooperative study with other Clinical Center personnel was undertaken. Gastric mucosal cytology studies following chymotrypsin lavage was undertaken; no results to report as yet.

Members of the Branch continue to be active in other collaborative projects. One of these is a study with the National Research Council and the Veterans Administration on the

natural history of multiple sclerosis. Our particular interest is that of the relationship of geography and climate to the prognosis of multiple sclerosis. A follow-up of army personnel who developed retrobulbar neuritis during World War II may reveal whether patients with early multiple sclerosis can be expected to have fewer exacerbations if they reside in a warm or southern climate.

This Branch continues with other activities in multiple sclerosis epidemiologic research. At the request of personnel of the University of Tokyo, who are receiving aid from the National Multiple Sclerosis, the feasibility of studies by Japanese scientists on the geographic distribution of multiple sclerosis in Japan is to be explored. The Branch Chief continues as a member of the Advisory Boards of the National Multiple Sclerosis Society and the Canadian Multiple Sclerosis Society.

The Branch maintains its interest but has little else to offer in the study by Dr. Carl Witkop, NIDR, among the "Wesorts" of Maryland.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT [illegible]

Part A. Project Description Sheet

1. **NINDB 23 (C)**
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology (NINDB); Biochem.Serv.(CC)
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Cytology of Gastric Mucosa and Other Studies among Amyotrophic Lateral Sclerosis Patients
PROJECT TITLE

7. Glen A. Drager, M.D.
PRINCIPAL INVESTIGATOR

8. Leonard T. Kurland, M.D., Dr. Katherine Herrold, Dr. Albert W. Hilberg, Mr. Pasco Del Vecchio
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH [illegible] ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

A. Objectives:

1. To determine if any abnormality exists in the gastric mucosal cells of patients with amyotrophic lateral sclerosis.

2. To evaluate magnesium serum levels among patients with amyotrophic lateral sclerosis.

B. Methods Employed: Gastric cells are stained by a modification of Papanicolaou following removal by gastric washing with chymotrypsin lavage technique.

C. Patient Material: Six patients at the Clinical Center, NINDB are expected to be studied. **(N-2-901)**

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(Attachment I)

SERIAL NUMBER

10. PROJECT DESCRIPTION (CONTINUED)

D. Major Findings: None yet reported.

E. Significance to the Program of the Institute: There is some question as to whether the hypothetical underlying metabolic defect is due to some gastric abnormality. This gastric washing technique had been tried on eight patients at the Mayo Clinic by one of the investigators (Dr. Kurland). No truly abnormal cells were noted. That study had to be discontinued when Dr. Kurland was transferred to the N.I.H. It had not been possible to determine whether the cells studied in these cases had not been properly collected and stained or whether there was some unknown factor responsible for rapid deterioration of the cells. A muscle biopsy is taken from each of the patients also.

F. Proposed Course of Project: If cells are normal with technique used here, project will be discontinued; if cells are abnormal, gastric biopsies and other studies will begin to determine basis for the abnormality.

Form No. ORP-1
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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 23 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 23 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 24 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPT.

4. NIH, PHS
SECTION OR SERVICE

5. VA Hospitals through U.S.
LOCATION (OTHER THAN BETHESDA)

6. Study of Natural History of Multiple Sclerosis
PROJECT TITLE

7. Benedict Nagler, M.D. (Chief, Neurology Div., Dept. of Medicine & Surgery, VA
PRINCIPAL INVESTIGATOR

8. OTHER INVESTIGATORS: Dr. Gilbert W. Beebe, Statistician, NRC
Dr. J. F. Kurtzke, Chief, Neurology Service
VA Hospital, Coatesville, Penna.
Dr. L. T. Kurland, Chief, Epidemiology Branch, NINDB

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PHS (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH

10. PROJECT DESCRIPTION

Objectives: In the absence of specific treatment, many patients with Multiple Sclerosis have been advised to migrate to areas of milder climate. The specific questions to be asked are:

A. For men with retrobulbar neuritis or optic neuritis only, is the likelihood of progression to Multiple Sclerosis associated with geography or climate?

B. For men with valid early diagnoses of Multiple Sclerosis, what is the prognostic significance of a wide variety of factors present at the time of onset, and of residence subsequent to onset?

C. Are there characteristics of background and of pre-service environment, or of military service, which are associated with significant increase in the likelihood that Multiple Sclerosis will be diagnosed during the period covered by World War II and two years thereafter (the statutory period of grace for service connection)?

Methods Employed

1. Selection of cases and controls

   a. It is proposed to screen admissions to VA Hospitals for retrobulbar neuritis and optic neuritis in the Army for the period 1942-1951, in the Navy for the period 1946-1951, and in the VA for the period 1949-1952, and to select from among them all men whose recorded findings meet the study criteria for retrobulbar neuritis of unspecified etiology. That is, cases in which there is a history of syphilis, other confirmed central nervous system disease, intoxication from methyl alcohol, thallium, carbon monoxide, arsenic or hydrocarbon solvents, will not be eligible for study here. In addition, review of the eligibility of the case will be made independently of any knowledge of either residence or subsequent medical history.

   b. All cases of multiple sclerosis diagnosed during World War II among service personnel and in veterans for the two years after discharge from the service at the end of World War II.

   c. A roster of "controls" consisting of a Service personnel selected by appropriate sampling techniques.

Significance to the Program of the Institute

We would hope to clarify an important practical question, i.e., the effect of geographic latitude or climate on the prognosis of multiple sclerosis. In addition, if significant variations in incidence are found to be associated with some geographic factor and if individuals from low prevalence areas were found to develop multiple sclerosis within a limited period of "exposure" in high prevalence areas, it might be possible to establish an approximate "incubation period" for this condition.

Proposed Course of Project

Study expected to require two years to complete.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 24 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT	TOTAL		PROF	OTHER	TOTAL
FY'57		0				0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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Calendar Year 1956

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 24 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 25 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5. Duxbury, Massachusetts
LOCATION (IF OTHER THAN BETHESDA)

6. Multiple Sclerosis in Duxbury, Massachusetts
PROJECT TITLE

7. Walter Deacon, M.D., Duxbury, Massachusetts
PRINCIPAL INVESTIGATOR

8. Leo Alexander, M.D., Boston, Massachusetts & L. T. Kurland, M.D., NINDB
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION

A. Objectives: Dr. Deacon had the impression that multiple sclerosis was highly prevalent in this community of 4200 persons. He had personally seen seven patients suspected of having multiple sclerosis last year. In his preliminary review, 17 patients were described. On follow-up in August 1956, only 12 patients were found to be residing in Duxbury. Others were not permanent residents in this area, had moved or died. Eleven patients were examined. Multiple sclerosis was considered as the diagnosis in five cases; three were considered as "possible" multiple sclerosis and the remaining three were thought to have hereditary ataxias. A brother of one of the latter died of multiple sclerosis, however.

B. Significance to the Program of the Institute: The prevalence rate for multiple sclerosis, based on diagnosed cases, in this small community is very high but does not differ by a statistically significant amount from that reported for Boston. No pattern by time or place of onset of cases was noted in the community. However, it is conceivable that the reported rate in the Boston area is appreciably lower than the "true" rate in the area.

PUBLIC HEALTH SERVICE - - [illegible] INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

10. PROJECT DESCRIPTION (CONTINUED)

C. Proposed Course of Project: A review of the cases in six to twelve months is contemplated.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 25 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATIVE	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 25 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 26 (C)**
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5. Charleston, S.C. - Medical College of South Carolina
LOCATION (IF OTHER THAN BETHESDA)

6. Epidemiologic Survey of Selected Neurologic, Myopathic & Ophthalmologic Disorders.
PROJECT TITLE A. Charleston, South Carolina Project

7. Oliver Rhett Talbert, M.D., Assistant Prof. of Neurology, Medical College of South Carolina, Charleston, S. C.
PRINCIPAL INVESTIGATOR

8. OTHER INVESTIGATORS: Milton Alter, M.D., Epidemiology Branch, NINDB (Sr.Asst.Surg.)
R. S. Allison, M.D., Prof. of Neurology, Univ. of Belfast Ireland.
L. T. Kurland, M.D., Epidemiology Branch, NINDB

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

A. Objectives: To obtain through collaboration with the Epidemiology Branch, NINDB (1) appropriate statistical data for selected neurologic, myopathic and ophthalmologic disorders; (2) to conduct appropriate epidemiologic and genetic investigations to explain the absence of undue concentration of cases in the community.

B. Method and Patient Material: (1) All local sources of medical information to be surveyed as follows: Practicing physicians to be queried regarding patients observed or treated over the previous five years for each of several groups of diagnoses. Medical student surveyors to assist in record abstracting at the request of each physician.

(2) For the previous ten years, abstracts for the selected diagnoses obtained from: Record systems in all local (and state mental or epileptic hospitals), clinics, nursing homes and departments of public health (medical care and mortality).

(3) Arrangements through the private physicians or the clinics to examine selected patients for classification.

(4) Statistical analysis for diagnostic groups to provide data on incidence, prevalence, mortality and life expectancy by appropriate population characteristics would be carried out.

(5) These data obtained from this survey and similar ones will be made available to the NINDB coordinating center for the comparative statistical study. The following groups of clinical diagnoses will be considered:

a. Severe congenital anomalies -- including myelodysplasias, encephalodysplasia, mongolism and congenital hydrocephalus.

b. Other nervous system conditions -- brain and spinal cord tumors, convulsive disorders, chorea, cerebral palsy, Parkinsonism, multiple sclerosis, lateral sclerosis, subacute combined degeneration of the cord, cerebroretinal degeneration, hepatolenticular degeneration, epiloia, the encephalitides, optic and retrobulbar neuritis, cerebellar degenerations and ataxias, tic douloureux.

c. Various muscular and neuromuscular disorders such as the myotonias, dystrophies, atrophies and myasthenia gravis.

d. Selected eye disorders -- such as tumors, glaucoma and cataract. The statistics on vascular disorders affecting the central nervous system and a few other groups are expected to be derived principally from mortality data.

C. Major Findings: None to report

D. Significance to the Program of the Institute: To provide basic statistical data which are needed in the field of neurology and ophthalmology. Evaluation of such data may result in further epidemiologic investigations to explain the absence of, or unusual concentrations, of cases which in turn should provide the basis for definitive laboratory or clinical research. Statistical data are also needed in planning for the best utilization and future needs of research and medical care facilities.

E. Proposed Course: The project will get under way during November 1956 and should continue through June 1958.

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October 1956
(Attachment I)

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 26 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

National Multiple Sclerosis Society providing funds to Medical College of South Carolina until February or March of 1957.

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(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 26 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 27 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5. Mariana Islands
LOCATION (IF OTHER THAN BETHESDA)

6. Amyotrophic Lateral Sclerosis, Other Neurological Disorders and Congenital Anomalies in the Mariana Islands
PROJECT TITLE

7. Samuel J. L. Pieper, Jr., Sr. Asst. Surgeon, Epidemiology Branch, NINDB
PRINCIPAL INVESTIGATOR

8. Leonard T. Kurland, M.D., Lorenzo L. G. Iriarte, Govt. of Guam, Dept. of Medical Services
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION

A. Objectives

1. To bring to completion, if possible, the various epidemiologic, therapeutic, genetic, and clinical studies of amyotrophic lateral sclerosis begun in 1953 and 1954 and

2. To determine the frequency and distribution of post-encephalitic Parkinsonism, other neurological diseases and congenital anomalies among the populations of the Mariana Islands.

3. Pregnancy in relation to amyotrophic lateral sclerosis. See reference #2, under Item 16.

4. To test a number of suggested therapies

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(Attachment I)

SERIAL NUMBER

10. PROJECT DESCRIPTION (CONTINUED)

B. Methods Employed: (ALS) House to house surveys will be conducted in an attempt to obtain more accurate statistical data (particularly age and sex distribution) in specified villages in Guam and Saipan. In view of inconclusive results obtained in an earlier study of genetic and environmental factors in comparison of controls and patients, further study and comparisons of Chamorros and Carolinians on Saipan are planned. Matters which we thought were satisfactorily answered, although of no significance in amyotrophic lateral sclerosis, will be excluded. Other factors such as toxic fish, diet, and family history will be more thoroughly studied. A follow-up of Japanese B encephalites cases previously studied by Professor W. McD. Hammon of the University of Pittsburgh is contemplated but final plans will be made after a pilot study of surviving cases. Other neurological and myopathic disorders and congenital anomalies will be looked for in the course of the house to house surveys.

C. Major Findings: See last year's report. No successful therapy.

D. Significance to the program of the Institute: See last year's report.

E. Proposed Course of this Project: It is hoped that this will be the final phase of this series of investigations of amyotrophic lateral sclerosis on Guam and other Mariana Islands. We shall attempt to determine whether congenital anomalies are more prevalent among offspring of potential amyotrophic lateral sclerosis patients.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 27 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,000	567	$10,567	1	0	1

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	0	1	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

U.S. Navy Bureau of Medicine and Surgery, Government of Guam, Department of Medical Services.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 27 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

(1) Kurland, L.T.: Investigations of Geographic Distribution of Multiple Sclerosis and Amyotrophic Lateral Sclerosis: Etiologic Implications. (In French) Acta Neurol. Psychiat. Belg. 56:287-301, 1956.

(2) Huston, J. Wilson, Lingenfelder, John, Mulder, Donald W., and Kurland, L.T.: Pregnancy Complicated by Amyotrophic Lateral Sclerosis. American Journal of Obstetrics and Gynecology 72(1): 93-99 (July 1956)

(3) Kurland, L.T., and Mulder, D.W.: La distribución geográfica de la "esclerosis en placas" y de la esclerosis lateral amiotrófica, con referencia especial a la población chamorra, en parte espanola, de las Islas Marianas. Revista Espanola de Oto-Neuro-Oftalmologia y Neurocirurgia . 83-84:127-137, 1956.

(4) Kurland, L.T., Mulder, D.W., Sayre, G.P., Lambert, E., Hutson, W., Iriarte, L.L.G., and Imus, H.A.: Amyotrophic Lateral Sclerosis in the Mariana Islands, A.M.A., Archives of Neurology and Psychiatry, 75:435-441, (April) 1956

(5) Kurland, L.T.: Epidemiologic Investigations of Amyotrophic Lateral Sclerosis. 3. Genetic Interpretation of Incidence and Geographic Distribution. Proceedings, Staff meetings of Mayo Clinic (To be Published)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 28 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPT.

4. NIH, PHS
SECTION OR SERVICE

5. Japan
LOCATION (IF OTHER THAN BETHESDA

6. Multiple Sclerosis and a few selected neurological diseases: 1. A preliminary study of various communities in Japan as to their suitability for future surveys
PROJECT TITLE

7. Yoshigoro Kuroiwa, M.D., or Shigeo Okinaka, M.D., Ph.D.
PRINCIPAL INVESTIGATOR

8. Hirotsugu Shiraki, M.D., Leonard T. Kurland, M.D. (consultant)
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

A. Objectives: To determine through an exploratory study whether further investigations of the prevalence of multiple sclerosis in Japan can be undertaken. A number of Japanese neuropsychiatrists have stated that multiple sclerosis is rare in Japan, although some American neurologists have described cases in Japanese.

B. Methods Employed: In this exploratory study, various communities will be visited to determine the feasibility of conducting the necessary surveys, the availability of neurologically trained or oriented physicians, the type of medical facilities, the presence of diagnostic classification of hospital and clinic records, the anticipated response for the desired information from the members of the medical society and public health officials to such a study.

C. Major Findings: None -- so far.

D. Significance to the Program of the Institute: If the surveys are undertaken, the data on frequency and geographic distribution could be compared with that in the U.S. It would be of interest to determine whether some racial difference exists and whether the frequency of multiple sclerosis is lowest in southern Japan.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 28 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

National Multiple Sclerosis Society is providing funds for Japanese physicians to carry out preliminary study.

Form No. CRP-1
October 1956
(Attachment I)

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 28 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None to date

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 29 (C)**
SERIAL NUMBER

2. NINDB, PHS
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Glaucoma Statistics for a Small Urban Community; A Pilot Study.
PROJECT TITLE

7. Leonard T. Kurland, M.D.
PRINCIPAL INVESTIGATOR

8. Dr. Robert Taub, Clinical Assistant in Ophthalmology - Northwestern University & Attending Ophthalmologist, Columbus & Children's Memorial Hospital
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

Bureau of State Services, Chronic Disease Program is planning to conduct glaucoma case finding surveys in the population.

10. PROJECT DESCRIPTION

A. Objectives: To determine the frequency of glaucoma by age and sex in the resident population of Rochester, Minnesota and to compare these rates with published reports for other populations.

B. Method and Patient Material: All diagnosed in Mayo Clinic records on previous ten years for resident population were abstracted. Latest residence and status of patients was determined. Prevalence rates determined on basis of living patients in the city.

C. Major Findings:

1. Chronic simple glaucoma more prevalent in females.

10. PROJECT DESCRIPTION (CONTINUED)

C. Major Findings (Cont'd)

2. Rate negligible below age 40 years; rises rapidly and consistently with age, so that by age 85 almost 3% of the population in this group have diagnosed glaucoma.

3. On the basis of case finding surveys in other areas, it is estimated that only half the existing cases of glaucoma in Rochester, Minn. have been diagnosed and are under treatment.

D. Significance to the Program of the Institute: The need for improved and simplified case finding methods to diagnose the estimated hundreds of thousands of undetected glaucoma cases in our population is emphasized. The project demonstrates the limited value of recorded data on glaucoma in usual medical sources of information. No evidence is presented for any particular population selectivity other than a slight difference in the rates by sex.

E. Proposed Course of Project: This pilot study is completed. The data will be used for comparison with similar studies which are contemplated.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 29 (C)**
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$12,500	568	$13,068	1	0	1

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
1	0	1	

FY'57

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Mayo Clinic, Rochester, Minnesota.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 29 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Frequency of Glaucoma in a Small Urban Community by Leonard T. Kurland and R. G. Taub. American Journal of Ophthalmology (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 30 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Frequency of Selected Neurologic and Myopathic Disorders in a Small Urban Community
PROJECT TITLE

7. Leonard T. Kurland, M.D., NINDB
PRINCIPAL INVESTIGATOR

8. Joseph Berkson, M.D., Mayo Clinic, Rochester, Minnesota
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION

A. Objectives: This project has been under way for two years. (See last year's report). Data are now being analyzed and reports on individual studies are appearing.

B. Proposed Course of Project. Data for numerous neurological disorders are still to be analyzed. The project is expected to require one additional year.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 30 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,650	568	$17,218	1	1	2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 30 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

(1) Kurland, L.T.: Cerebral Palsy Epidemiology Studies. 1. Aims, Definitions, Available Statistics, and Recommended Procedures (Presented at the American Academy of Cerebral Palsy 11/18/56) To be published.

(2) Kurland, L.T.: The Incidence of Intracranial and Intraspinal Neoplasms in a Small Urban Community (In preparation)

(3) Kurland, L.T.: Epilepsy in a Small Urban Community. (In preparation).

(4) Kurland, L.T. and Berkson, J.: Selected Neurologic and Myopathic Disorders in a Small Urban Community. (In preparation).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 31 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPARTMENT

4. NIH, PHS
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Congenital Anomalies in Motor System Disease
PROJECT TITLE

7. Leonard T. Kurland, M.D.
PRINCIPAL INVESTIGATOR

8. Ntinos Myrianthopoulos, Ph.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION

A. Objectives: To determine if certain hand, ear and other skeletal deformities in individuals in families with a hereditary amyotrophic lateral sclerosis have any relationship to the amyotrophic lateral sclerosis itself.

B. Methods Employed: Pedigrees of two families in which both amyotrophic lateral sclerosis and the congenital anomalies have been observed are being completed. Examinations, photographs and Xrays of affected individuals have also been completed.

C. Major Findings: In each family, two first cousins have similar ear deformity (partial to near complete absence of left ears and external auditory meatus. In same family, there are three second cousins of the above with a deformity of the second and third fingers of both hands with shortened and deformed phalanges. Rate of bone growth also appears abnormal on the basis of delayed appearance of wrist ossification centers in the affected twin of a dizygotic pair.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

10. PROJECT DESCRIPTION (CONTINUED

D. Significance of the Program to the Institute: Similar congenital deformities have been described in relation to hereditary ataxia families. These findings suggest some genetic relationship of the amyotrophic lateral sclerosis and the hereditary ataxias. Whether this study will shed some light on the mechanism of certain congenital anomalies remains to be seen.

E. Proposed Course of Study: These findings are responsible for our attempt to compare the prevalence of such anomalies among the Chamorros and Carolinians of the Marianas.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 31 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLICATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,650	568	$ 17,218	1	1	2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	1	2	

13. BUDGET ACTIVITY:

RESEARCH	[x]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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October 1956
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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 31 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

One article being readied for publication in near future

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 32 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Epidemiology
LABORATORY, BRANCH, OR DEPT.

4. NIH, PHS
SECTION OR SERVICE

5. California
LOCATION (OTHER THAN BETHESDA)

6. Investigation of Amyotrophic Lateral Sclerosis, Epidemiologic:
Amyotrophic Lateral Sclerosis among Chamorros of California
PROJECT TITLE

7. Leonard T. Kurland, M. D., Dr. P.H.
PRINCIPAL INVESTIGATOR

8. OTHER INVESTIGATORS: Jose Torres, NINDB
Lorenzo L.G. Iriarte, M.P.H., Dept. of Medical Services, Govt. of Guam

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PHS (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH

None

10. PROJECT DESCRIPTION

A. Objectives: To determine whether ALS continued to be highly prevalent in Chamorros (natives of Guam and other Mariana Islands) who had migrated from their native environment to California.

B. Methods: Attempt to develop roster of all Guamanians living in California through local Guamanian association and contacts. Interview and observation of all adults. Examination of persons suspected of having neurological diseases. Location of other cases among Guamanians in the continental U.S. through U.S. Navy and VA facilities.

C. Major findings: 165 adult Guamanians were located and interviewed in California. Among these, two were found to have ALS (1.2%). The rate among adults on Guam -- about 1%. (Rate in Caucasian U.S. population about 1 per 10,000). In addition, we learned of two brothers who left Guam in 1885 and developed ALS about 25 years later in San Francisco. Information was obtained on three ALS deaths in service personnel and one Guamanian woman who had lived in California for several years, among the small

SERIAL NUMBER

10. PROJECT DESCRIPTION (Cont'd)

C. Major findings (Cont'd)
(but indefinite) number of Guamanians who migrated to U.S. up to 1950. No. "second generation" Guamanian adults were located in the California study.

D. Significance: Further evidence that the underlying etiologic factor responsible for the high incidence of ALS on Guam, may be genetic and not environmental.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 32 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57	$12,500	567	$13,067	1.	0	1

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
1	0	1	

FY'57

13. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ PROFESSIONAL & TECHNICAL ASSIST- ☐

BIOLOGIC STANDARDS ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 32 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Kurland, L.T.; Torres, Jose & Iriarte, L.: Amyotrophic Lateral Sclerosis among Guamanians in California (To be published)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ANNUAL REPORT
SURGICAL NEUROLOGY BRANCH
NATIONAL INSTITUTE OF NEUROLOGICAL DISEASES
AND BLINDNESS

Calendar Year 1956

SUMMARY

During the period described by this report we have studied 201 patients on the wards. The average time in hospital was five weeks. In the Out-patient Department 161 patients were examined in a total of 259 scheduled visits. In the operating room we completed 261 procedures. Of these 39 included extensive electrical explorations of the cortex and subcortical structures. While 24 operations were performed for cerebral neoplasia. This clinical material, supported by laboratory work, provided the basis for 17 reports which were prepared for publication.

The majority of patients studied were epileptics. On the wards a new system of patient-observation has been established. This is designed primarily for observation of spontaneous seizures. As in the past, ward observation of spontaneous attacks has again provided useful information. It seems clear that temporal lobe seizures are characterized by a peculiar sequence of movements. These begin in face and jaws and continue with posturing of the extremities. Often, the first movements occur on the same side as the origin within the temporal lobe.

The most frequent warning of these attacks is epigastric. This aura is always accompanied by autonomic changes such as flushing, pallor, sweating, tachycardia and respiratory arrest. Gastric motility may be altered, as well. Since the patients relate this epigastric sensation to fear, we are trying to duplicate it by adrenalin injection.

The behavior of these patients is bizarre during some attacks and abnormal between all attacks. The ictal behavior can be changed by verbal stimuli when the focal origin is in the dominant hemisphere. The inter-ictal behavior is characterized by mood fluctuation, perseveration of ideas, abnormal speech and unusual interpretations of present experience. Occasionally it is punctuated by aggression and violence. It is quite similar to that which Bleuler described as paranoid schizophrenia. It differs from his descriptions in the absence of systematized delusional patterns.

The ictal behavior (in temporal lobe seizures) has been viewed as a fractionation of consciousness. We regard it from this viewpoint, and in order to broaden our perspective we have studied alterations of consciousness in tumours of the brain stem, narcolepsy, cataplexy, centrencephalic seizures and hypoglycemia. In one case of brain stem tumour, progressive alteration of consciousness seemed to be related to rostral progression of the neoplasm. Intracranial pressure was normal during this dampening of consciousness. In cataplexy the patient remains mute and immobile but he can understand speech and calculation is unimpaired. The hypoglycemic state began with euphoria and flight of ideas and ended in coma.

Fluid and electrolyte problems after hypophysectomy have been studied. These studies have stimulated a further consideration of such factors in cases with focal cerebral lesions.

Intractable pain, paresthesias and phantom limb sensations have been observed as well. One case of intractable abdominal pain which did not resolve after chordotomy and root section has responded satisfactorily to section of the dorsal cord. Some cases of head pain have found relief after occipital nerve section. The phantom limb sensation has been viewed as a disturbance of body image mechanisms. With this perspective, our artist has reconstructed the phantom from patient descriptions and followed their modifications after section of peripheral nerve and spinothalamic tracts.

Some aspects of cerebral palsy have been noted, and various neurological and psychological information has been obtained from these cases. One case of craniopagus has been studied. After ward observation, it was examined in the operating room.

In the operating room we have explored frontal, temporal, occipital and parietal cortices by electrical stimulation. Temporal cortex seems to contain sensory representations and the periamygdaloid region contains motor representations for face and jaws. Hypothermia seems to reduce cortical response to electrical stimulation and reduction in temperature also effects brain volume, colour, consistency and intracranial blood pressure. Low temperatures reduce the gross volume of arteriovenous malformations but have little effect on brain pressure related to other neoplasms.

There have been some technical developments in the operating room. Dr. Van Buren has devised a method for insulating instruments against spread of electrocautery discharge. Miss Lewis and Mr. Debroske have designed an operating table which supports two infants simultaneously. Miss Lewis has also designed drapes for this table. She has studied effects of zepharin on the brain as well as the use of detergents in neurosurgery. We have modified power-driven instruments and Mr. Debroske is developing a new instrument driven by sound impulses. In addition, we have designed a method for cold coagulation and tested this on small animals. Finally, we have planned a new operating suite with original designs for patient care and scientific observation.

In the laboratory, Dr. Li has studied the response of motor neurones and denervated muscle to micro-stimulation. He also is investigating the latency in response which occurs after stimulation of the amygdala. He has designed a method for remote stimulation of implanted electrodes and a series of electrical stimulations for the human operating room. Dr. Van Buren continues his observations on the visual pathway in monkeys and chimpanzees. These studies support clinical observations of the effects of temporal lobectomy on the visual fields. Dr. Klatzo is analyzing histochemical changes in epileptogenic lesions. With Doctors Laskowski and Piraux, he is studying experimental epilepsy in certain

mice. He is also producing epileptogenic lesions by direct application of low temperatures. In addition, he and his colleagues are analyzing effects of air exposure on brain substance.

Dr. Hall is studying the changes in respiration and blood volume which occur in hypothermic states. He has begun an extensive study of respiratory changes after cerebral lesions.

Dr. Frost has continued his interview-observation of patients with temporal lobe seizures.

Dr. Dekaban is studying the developmental anatomy of congenital cerebral lesions. He is collecting a large series of such specimens.

In the laboratory of primate neurology we have studied the effects of low temperature on epileptic discharges in the limbic system and on the electrical activity of the frontal and central cortex. Likewise the effect of direct application of low temperatures on frontal cortex has been noted. Epileptogenic lesions have been created in the temporal lobes of two chimpanzees and in the central cortex of another. We have recorded firing from the temporal scalp of two animals and observed clinical seizures in all. The effects of bilateral temporal lobectomy have been observed in three chimpanzees. Also, we have watched the effect of isolation and lysergic acid on normal and abnormal chimpanzees. Apparently these conditions do not effect chimpanzees after bitemporal lobectomy. They cause striking effects in normal chimpanzees. Miss Lewis continues her study of hierarchy and group activity in the chimpanzee colony. She is now studying their vocalization patterns as well. She has begun a study of primate fingerprint patterns. (In this connection it is interesting that Professor Purkinje was the first European and perhaps the first person to make a formal report on the significance of digital patterns.) Dr. Hall is collecting blood specimens from the chimpanzees in order to study their hematology in health and disease. We are collecting gross anatomical specimens as they become available.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 33 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Effect of Lesions of the Optic Pathways Upon the Geniculate Body
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: Since the visual field changes following temporal lobectomy have been carefully observed in another study of this series, it has been thought of interest to study the geniculate representation of this visual field change. As far as the author is aware, no previous studies of the geniculate body following temporal lobectomy in man have been carried out.

Method Employed: The geniculate bodies are serially sectioned and stained with cresyl violet, Heidenheim and neurofibral methods. The cresyl violet slides are photographed at 35 x magnification. The degenerative areas can be mapped on these prints. Tracings are made of these prints, and the cell population is indicated by varying the density of stippling on these tracings. These diagrams can then be reduced very considerably in size to permit publication and still leave clearly an indication of the cell population in all layers.

Patient Material: (N-12-520)

		No.	Average Stay - days
Admissions:	Adult Male	3	-
	Adult Female	3	

PROJECT DESCRIPTION (Continued)

Major Findings: The human material to date consists of two cases with temporal lobectomy, one case with damage to the optic radiation passing to the superior lip of the calcarine fissure with visual fields, one case in which infarction of the posterior cerebral artery had affected only the lower anterior portions of the calcarine cortex, one case with amputation of the posterior occipital lobe with visual fields and two cases of pregeniculate lesions both with visual fields.

Reconstructions have been completed in the two cases of temporal lobectomy and the single case of damage to the radiation passing to the superior calcarine lip. Damage to the temporal portion of the optic radiation was found to lie in the posterior two-thirds of the geniculate body and in that portion of the geniculate body which lies lateral to its apex. The degeneration was seen to extend through all layers but not into the magno-cellular portion. The degeneration, unfortunately, was not clear cut in these cases and is somewhat difficult to trace.

The case of the upper parietal lesion (an inferior homonomous quadrantanopia by visual field) degeneration and gliosis is seen in the middle third of the geniculate body but on that portion medial to the apex of the geniculate body. These three cases therefore indicate a rough areal distribution of the radiation within the geniculate body. The fact that the apex of the geniculate body is degenerated in lesions which do not affect macular vision clinically suggest that this portion does not contain macular representation. This contradicts the diagrams of Polyak.

The remaining human material has not been completed. However, in the case of a mid-chiasmatic pregeniculate lesion of long duration, it was interesting to note that as opposed to the radiation lesions, the degeneration in the lateral geniculate body is laminar in character similar to that from enucleation of an eye. However, since the crossing fibers on each side are destroyed the lesion in the two geniculate bodies is quite symmetrical. Unfortunately, only a small portion of the geniculate bodies in this case is available for examination, so a complete reconstruction cannot be made.

Preliminary examination of the geniculate bodies of a severe lesion of the optic pathways at the level of the chiasm some 70 days prior to death showed no striking degeneration. This is as opposed to the retinae in which degeneration was far advanced.

Significance to Neurological Research: This study is intended as a further approach to clinical anatomical correlation of visual function in man.

Proposed course of project: Collection of human anatomical material will continue as it presents. The brain of one chimpanzee in which bilateral temporal lobectomy had been carried out is presently available for study, and reconstructions will be made from these geniculate bodies. Since the macula representation in the calcarine cortex is supposed to lie at the posterior extremity of the occipital lobe the case in which a posterior occipital lobectomy was carried out some three months prior to death this may possibly give evidence as to the macular representation in the lateral geniculate body. Understanding of this representation would obviously be of great interest.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 33 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
TY'57	$7,750	5,152	$12,902	.33	.66	.99
	BUDGETED POSITIONS			PATIENT DAYS		
	PROF	OTHER	TOTAL			
FY'57	.33	.66	.99			

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 33 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 34 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Studies of Involuntary Movements
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: At the present time there is no adequate explanation of the cause or mechanism of production of involuntary movements. It is hoped by careful correlation of clinical findings, recording of the electrical activity of deeper structures at operation and study of the anatomical material may provide new information on this subject.

In order that recordings can be made from the basal ganglia and coagulation carried out here if indicated, a stereotaxic instrument is needed to guide the electrode. Since the available designs seemed inadequate in some respects, development of a new instrument has been undertaken.

Method Employed:
1. Clinical observation.
2. Photographic techniques.
3. Analysis by illustration of movement phases.

PROJECT DESCRIPTION (Continued)

Patient Material: (N-7-509)		No.	Average Stay - days
Admissions:	Adult Male	3	54.71
	Adult Female	1	38.33
	Children Male	1	
	Children Female	1	

Outpatient: Number of patients: 4
Number of visits: 8

Major Findings: After consultation in New York and Philadelphia where stereotaxic instruments for human use are presently employed, it became apparent that the present designs had several disadvantages. It was decided that a satisfactory stereotaxic instrument should imbody the following characteristics: (1) It should use rectolinear coordinates, to permit use of a standard brain atlas such as that per Spiegel and Wycis (2) the instrument must be zeroed by x-ray control and moved in relation to fixed points in the brain itself since bony landmarks are unreliable (3) it must permit electrode insertion at any angle in order to reduce to a minimum the length of the needle track and possible damage to vital structures (4) any point in the thalamus or basal ganglia should be reached through a single burr hole without having to recalculate angles of electrode insertion or do any more than move the three rectolinear coordinates of the electrode carrier (5) it must be possible to place and replace the instrument upon the skull in precisely reproducible positions so that it is not necessary to repeat the ventricular visualization with each placement of the instrument.

By the use of what is apparently a new principle in electrode carrier design, all the above requirements seem theoretically to have been met. In the past year, the design has been completed, the final plans finished for construction of the instrument which is presently taking place.

Significance to Neurological Research: Diseases which cause involuntary movements are not understood and cannot be treated effectively. These studies will constitute a step toward increased understanding in this field.

Proposed course of Project: The techniques of observation will be applied to selected patients and some of these patients will be treated by interruptions of the pathways which subserve motion. Wherever possible, we will make an anatomical analyses of the available material and correlate these findings with clinical observations. Likewise, we will begin correlation of this data with observations made at the laboratory on experimental animals.

Following completion of the stereotaxic instrument, it is planned to test its accuracy upon opaque objects placed within the dried skull and localized as would be the case in the living patient by x-ray. If these studies show the apparatus to be reliable it is planned to carry out ventriculography in cadavers and localize areas in the basal ganglia and brain stem which will be marked by dye. When the brain is cut, it will be possible to estimate the localization error of the instrument and determine whether it is reliable enough for patient use.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 34 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	$17,558	$25,308	.34	.66	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.34	.66	1.	200

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 34 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 35 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Visual Field Deficits Following Temporal Lobectomy
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE, (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: This study is directed toward the definition of the precise course of the visual fibers in the temporal lobe. The precise relationship between the fibers of the visual radiation passing anteriorly in the temporal lobe and the retinal areas which they supply has been previously worked out only in a gross manner by the use of patients with neoplasms of the temporal lobe.

The availability of patient material in which the temporal lobe has been removed for epilepsy offered a unique opportunity for the restudying of the problem in patients where the removal was made in a relatively quantitative fashion and in which the effects of inactivation by compression, as may be found about a cerebral tumor, could be eliminated.

Method Employed: Both prior and following operation the visual fields were examined both on the perimeter and on the tangent screen with a variety of test objects. Particular attention was paid to the visual field defect. In each case this density was determined by the use of a test object as required up to 10 inches in diameter.

PROJECT DESCRIPTION (Continued)

The relationship of the quadratic field defect to macular vision was also carefully tested by the use of small white or small colored objects. The visual acuity in all cases was carefully tested. Every opportunity has been taken to re-examine patients at a considerable period following temporal lobectomy to rule out changes due to post-operative swelling which might appear in examinations made within the first month following operation.

Patient Material: (N-1-503)

		No.	Average Stay - days
Admissions:	Adult Male	15	11.07
	Adult Female	13	6.46
	Children Male	3	17.0
	Children Female	1	3
Outpatient:	Number of patients:	10	
	Number of visits:	10	

Major Findings: The visual fields in 41 cases of temporal lobectomy for epilepsy have been studied for evidence regarding the fiber architecture of the anterior portion of the optic radiation. The evidence suggests that the visual field defects in these cases are the results of the lesion solely of the optic radiation. Visual field defects were found (1) not to affect visual acuity (2) not to alter the size of the blind spot (3) to have sloping inferior margins (4) to pass over the horizontal meridian (5) to have a density in the defect roughly porportional to the perpendicular distance from a line paralleling the inferior margin of the defect and passing through the fixation point (6) to be both congruous and incongruous but if incongruous to have the larger defect of the visual field in the eye on the side of the lesion. In terms of the physiological - anatomical correlation, these findings were explained respectively as follows: (1) One half of macular vision is sufficient to permit normal visual acuity (2) alteration of one field of vision does not entail a change in the visual projection of the remaining intact retina, (3) the fibers from adjacent retinal elements are spacially separated in the optic radiation (4) the representation of the upper and lower quadrants in the optic radiation are not separated by macular fibers (5) the macular representation lies medial to that of the peripheral retina (6) in the anterior portion of the optic radiation, the representation of the ipsilateral and contralateral retinal halves both extend an equal distance anteriorly, but the ipsilateral retinal representation lies lateral to the contralateral retinal representation.

Significance to Neurological Research: Up to the present time, it has been assumed in the literature that the homonomous portions of the retinal representation come to lie together at the level of the geniculate body then pass together throughout the optic radiation. This study gives evidence that the representation of the homologous retinal areas are indeed separated in the temporal portion of the optic radiation and do not come together until the occipital portion of the optic radiation is reached. Furthermore, the sloping inferior margins of the visual field defects must indicate that there is spacial separation of homologous retinal fibers in the optic radiation.

PROJECT DESCRIPTION (Continued)

Proposed course of Project: The first manuscript, "Architecture of the Optic Radiation in the Temporal Lobe" by J. M. Van Buren, M. D. has been prepared but requires further revision before being submitted for publication in the journal BRAIN.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 35 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	$26,073	$33,823	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.66	.99	297

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 35 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 36 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Pain Mechanisms
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. K. Hall, M. D. and F. Norris, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: The essential interest of this study is centered upon methods for evaluation of pain with its ultimate goal being a quantitative evaluation of the pain from which the individual is suffering. Depending upon the degree to which the primary aim of the study is achieved the following studies can be undertaken: (1) evaluation of the standard surgical procedures for relief of pain (2) evaluation of standard medical procedures for relief of pain (3) the surgical approach to pain pathways may be expected to provide an opportunity for study of surgical lesions of the central nervous system which will be exploited as far as possible as the opportunity arises.

It is hoped by personality studies by psychometric methods and a study of the autonomic responses of the patient that some sort of objective evidence that can be compared from patient to patient can be achieved to help in the quantitative evaluation of pain. The psychometric methods at the moment consist in the Rorschach test and the Minneapolis Multiphasic Personality Inventory. The study of autonomic phenomena is dependent upon the development of a Polygraph. This instrument will measure the blood pressure by an ausculatory method (no arterial puncture) electrocardiogram, the respiratory rate and pattern, the skin resistance, the pressure variations from the plethesmograph, and pressure variations of hollow visi, such as the bladder or stomach. By the simultaneous recording of these autonomic responses, insight may be gained as to the nature of the pain response.

PROJECT DESCRIPTION (Continued)

Pain will be produced by an electrical shocking apparatus. Whether it is possible to develop this apparatus to a point where pain can be delivered in easily reproducible amounts remains to be determined.

The study of surgical lesions of the central nervous system undertaken for pain relief will include sweating tests and cystometrograms.

Patient Material: (N-6-512)

		No.	Average Stay - days
Admissions:	Adult Male	7	44.43
	Adult Female	4	38.50
	Children Male	-	
	Children Female	-	
Outpatient:	Number of patients:	18	
	Number of visits:	28	

Major Findings: At the present time psychometric tests are being collected for comparison with the result of repeated interviews and examination of the patient on the ward for personality evaluation. A pilot review will be carried out following the accumulation of 10-15 cases to determine whether modifications should be made in this method or whether the method should be continued.

In the past year, all the components of the Polygraph have been assembled, and have been sent to the electrical shop for assembly. It is now estimated that the polygraph will be available for use on the ward sometime in November 1956.

Significance to Neurological Research: There is preliminary evidence that the autonomic responses to pain and other stimuli in patients suffering pain is enhanced. This will be investigated as the possible basis for objective assessment of the individual's response to pain.

Proposed course of Project: The major hurdle at the present time consists in the completion of the polygraph for autonomic recording. The major part of the patient load has therefore been held up, but when this instrument is ready it is hoped to admit more patients for study.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 36 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57 $7,750	$40,734	$48,484	.33	.66	

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	464
FY'57 .33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 36 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. **NINDB 37 (C)**
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Effect of Tumors Upon Central Nervous System Function and Structure
PROJECT TITLE

7. John M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. M. Baldwin, M. D. and Philip Rubin, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: This study has a dual aim: 1) to carry out physiological-anatomical correlations in man, 2) to evaluate the effects of newer methods of treatment for tumors of the central nervous system. In the present program attempt will be made to utilize the intrusion of disease upon the central nervous system of man as an "experimental" lesion.

Although much can be accomplished through animal experimentation in determining the function of structures within the nervous system it is apparent that the need for confirmation of these findings in man is ever present. In addition, studies of function which cannot be properly evaluated in animals (e.g., sweating) must be carried out in man. Although the fruits of a study of this type are of widespread nature, particular attention has been placed upon three major features: (1) To note the effects of neoplasm upon the function of the optic pathways of man and particularly upon the correlation of the visual fields and the anatomical changes in retina, geniculate body and calcarine cortex, (2) To study, particularly in cases of slowly expanding lesions of the upper brain stem, the effects of these lesions upon personality, consciousness and the electroencephalogram. Since the majority of these lesions are of terminal nature, opportunity

PROJECT DESCRIPTION (Continued)

therefore will arise for clinical-anatomical correlation.

Method Employed: The evaluation on a clinical basis of the position and nature of the tumor will be determined as can best be done by history, neurological examination, contrast examinations, and surgery. The symptoms under consideration will be evaluated using largely clinical methods, although it is hoped that the polygraph needed for autonomic evaluation will be of aid in this direction. In the post-mortem examination, careful serial examination of the involved structures will be undertaken both grossly and microscopically and charts prepared from this material. By the use of these charts and the method of overlapping areas it is hoped that features of localizing anatomical significance may be discovered.

Patient Material: (N-12-514)

		No.	Average Stay - days
Admissions:	Adult Male	17	51.32
	Adult Female	23	31.15
	Children Male	1	129
	Children Female	-	
Outpatient:	Number of patients:	19	
	Number of visits:	48	

Major Findings: Clinical Aspects: The principal investigator has gained experience on the ward and operative management of patients with increased intracranial pressure. Two minor changes of technique have been introduced which have been found of value. (1) A thermostable tough plastic covering which is applied like enamel has been found with which instruments used for coagulation can be coated. This is of particular value since it allows coagulation of deeply placed points (for instance the stalk of the pituitary gland) which are surrounded by important structures which might otherwise be hurt by the coagulating current. (2) A modification of the ventriculoperitoneal shunt technique has been devised and has been used successfully in one case. This consists of the use of a number 10 French rubber catheter for the actual cannulation of the ventricle. The use of this cannula has the advantage in that it will easily slip down the tract made by ventricular puncture needle, and thus avoids additional trauma incurred by the use of a largergauge tubing. At the level of the skull an anatomoses is made between the catheter and the usual 5 mm. gum rubber tube which is passed subcutaneously to the peritoneal cavity by a stainless steel connecting tube which is wired firmly to the skull. It is thought that this may be mechanically better than the older method since the ventricular catheter is fixed in place to the skull and cannot subsequently be withdrawn or moved by any motions of the patient. A possible objection may lie in the relatively small diameter of the ventricular catheter which may lead to clogging if there is free floating debris in the spinal fluid. Whether the method is practical or not will have to be determined by future cases.

Physiological-Anatomical Aspects: (1) Sweating tests: During sweat test, it has been observed that the sequence of events is as follows: There is initial warming of the fingers and toes (even though these may not be exposed to the heating agent followed by rise of pulse and respiration and finally sweating. The rectal temperature does not rise under normal circumstances with the outbreak of sweating. When, however, the sweating response is restricted as for instance, with a high paraplegia, the vaso

PROJECT DESCRIPTION (Continued)

dilatation response is lost in the paralyzed extremities and the rectal temperature rises early. One interesting case of the brain stem glioblastoma was observed in which there was progressive loss of the sweating response over the months from the feet upward and a few weeks before the patient's death, sweating was restricted to the upper chest and head. As might be expected, the patient's temperature rose early in the testing. (2) Anatomical data: See projects 516, 518, 519 and 520.

Significance to Neurological Research: Neurophysiological data in animals is extensive but research of this type if it is to be helpful in the evaluation or treatment of human disease must be confirmed in man. Since critical evaluation of vision, personality and consciousness cannot be made in animals and the human EEG is species specific in type, re-evaluation of these phenomena in man is necessary. The new surgical-radiotherapeutic techniques have not as yet been carefully investigated in any considerable series of tumors of the central nervous system.

Proposed course of Project: The accumulation of a large number of cases for a study of this type in which overlapping areas of involvement must be charted is imperative before results of any reliability can be achieved. Thus our present problem is one of collection of data.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 37 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	$150,030	$157,780	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.66	.99	1709

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 37 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Baldwin, M. Chapter on "Space-Occupying Lesions of the Central Nervous System," PRACTICE OF MEDICINE (Sixth Edition), J. C. Meakins, editor, St. Louis, 1956, The C. V. Mosby Co., p. 1671.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 38 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Study of the Adult Human Retinal Cytology using Golgi and Chromatic Methods
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: This study of normal retinal cytology is undertaken as a basis for the evaluation of degenerative lesions in the retina. As far as can be determined, no previous work has been carried out using the Golgi method in the adult human retina. A considerable portion of the available reports of retinal cytology are confused by post-mortem artifact. By the use of early retinal fixation these artifacts may be eliminated.

Method Employed: The study will be carried with human retinas fixed within half hour of death by intra-ocular injection of formalin. Some will be stained by the Golgi and others by chromatic methods.

The Golgi method will be used primarily for study of the conformation of individual retinal elements, while the chromatic methods will be used primarily for the study of retinal cyto-architecture. In the latter connection, serial sections will be made of the eyes, and from these, 2 dimensional reconstructions of the retina and its various cell fields can be made.

The vital methylene blue method has been investigated and applied in six Macaque monkeys and one chimpanzee in order to learn at first hand the nature of these retinae which so closely approach that of man in structure. It is hoped that at some future date to have an opportunity

to undertake this method of staining in the human eye prior to enucleation.

Patient Material: (N-12-518)

		No.	Average Stay - days
Admissions:	Adult Male	1	-
	Adult Female	2	6.5
	Children Male	0	
	Children Female	0	
Outpatient:	Number of patients:	0	
	Number of visits:	0	

Major Findings: With patient searching through the Golgi slides, it is proved possible to find isolated retinal elements in the adult human retina which are suitable for photography and a number of these elements have thus been recorded. Due to incrustation of precipitate upon the vitreal aspect of the retina the ganglion cells have been the most difficult to adequately observe.

Using the chromatic methods, it has been possible to serially section the eyes of three further patients during the past year who had normal visual fields prior to death. The reconstruction from the sections of the two-dimensional plan of the human retina remains to be carried out.

The not infrequent displacement of ganglion cells and other retinal elements outside their commonly accepted zone has been confirmed in much of the present material.

A close study of the retinal cell population in the chimpanzee retina has by the methylene blue technique shown some points which may be new. It appeared that more than one body having a well defined membrane and a translucent though not entirely opaque central portion may be found in the nucleus and closely resembles multiple nucleoli. This was a most curious finding and must be further investigated. Number of small bodies have been stained in the dentites of the ganglion cells which have not been previously illustrated by either Cajal or Polyak. It remains to be determined whether these are artifacts. Two types of ganglion cells have been seen which in addition, do not seem to be described by the above authors. In one, branching occurs at obtuse angles very close to the cell body and processes of the dentites do not extend over 10 soma diameters from the cell. These cells send their axones into the near fiber layer. There are, in addition, very rare cells with fewer processes nearly non-branching which spread for tremendous distances over the retina and do not obviously send an axone into the nerve fiber layer although they appear to lie in the lower portion of the ganglion cell layer. Their identity remains in doubt since they do not appear to resemble either the amacrime cells or horizontal cells previously described nor do they resemble the conventional pictures of the ganglion cells.

It has become apparent that in the study of retinal histology by the spread technique that all cell types must be related to their distance from the fovea. The above-mentioned types of ganglion cells are seen only in the periphery. With this in view, a system has been devised of making large drawings of the retinal spread preparations and on these indicating each area from which a particular photomicrograph was taken. Thus, will later

PROJECT DESCRIPTION (Continued)

be possible to collect the histological photographs and better evaluate the aerial distribution of cell types in the retina.

Significance to Neurological Research: Although Golgi studies of retinae in low animals has been carried out, it seems desirable to confirm the cytological findings in man. Such an opportunity now presents itself.

A further study in the normal variants in the human retina is necessary to determine the limits of normal.

The correlation between the anatomical configuration of the retina and the visual field is obviously of basic importance to the proper evaluation of visual field studies.

Proposed course of Project: More human autopsy material is desirable. The methods as devised above have proved satisfactory and must be applied to more cases. Further reconstructions must be made in cases of serially sectioned retinae presently available.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 38 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 38 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 39 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Effect of Lesions of the Optic Pathways Upon the Retina
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: Study will be made of the effects of degeneration upon the areal pattern of ganglion cells in the retina by the use of reconstruction technique. Attention will also be paid to other retinal layers to determine the degree of transynoptic and transneuronal degeneration. As far as the author is aware, only one case of retinal degeneration following a lesion of the pregeniculate pathway has been reported in man. In no instances have retinal changes from postgeniculate changes been recorded in man, although Polyak has recorded one instance to the author's knowledge in a monkey. Human material is presently available for evaluation, and lesions have been placed in macaques some 24 months ago, which are presently ready for study.

Method Employed: The eyes were fixed by intra-ocular injection of formalin, marked for orientation on the slide, imbedded in paraffin and serially sectioned. Degenerated areas were marked out with ink on the slides, the slides projected at 35x magnification and traced upon paper. The degenerated areas on the tracing were measured, then from these measurements a two-dimensional reconstruction made. Conversion of retinal distances to degrees of visual angle permitted the superimposition of the areas of degeneration upon the clinically recorded visual field.

PROJECT DESCRIPTION (Continued)

In two macaques with lesions of the optic tracts intravital staining with methylene blue of one eye was undertaken.

Patient Material: (N-12-519)

		No.	Average Stay - days
Admissions:	Adult Male	1	-
	Adult Female	2	-
	Children Male		
	Children Female		

Outpatient:	Number of patients:	0
	Number of visits:	0

Major Findings: In monkeys, we have previously found hemiretinal degeneration following section of the optic tracts has been confirmed and indeed by the methylene blue technique has been shown that this can be easily and rather nicely demonstrated by spread preparations.

In animals with optic tract lesions of 18 months duration, secondary degeneration has been found in the bipolar cell layer leaving large cavities in this layer as well as the complete loss of the ganglion cells superficial to it. This is of some interest because this "cavitary atrophy" in some textbooks, at least, is ascribed to arteriosclerotic vascular change in the instances where it is found in humans. Since the lesions are made in the optic tract, it is obvious that this cannot be due to a circulator disturbance and is secondary simply to degeneration of the neuronal pathways.

As has been found in the study of the normal retina, it is becoming increasingly apparent that pathologic changes must be related to the distance of the point in question from the macula since there are such marked variations in the areal anatomy of the retina. In man 75 days has been found sufficient to permit complete ganglion cell degeneration in the retina following injury to the optic chiasm. It thus appears to correlate with the course of clinical pallor of the optic discs.

In an instance of pregeniculate damage to the optic pathways with retention of vision in one quadrant of the visual field and a visual acuity of 20/60, it has been found that the retention of a ganglion cell layer three cells thick in the appropriate retinal area just outside the fovea was sufficient to permit this degree of vision.

Significance to Neurological Research: These studies of purely destructive regions of the geniculate optic pathway are intended to elucidate the pathological changes in the retina following such a lesion. A clinical anatomical correlation is believed of basic importance for the understanding of the significance of visual field studies.

Proposed course of Project: Although there is no lack of animal material, every possible advantage will be made of additional human material as it presents itself. It is felt that the major emphasis

must be upon human material as this is an unexplored field.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 39 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	5,152	$12,902	.33	.66	.99

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 .33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP=1 Calendar Year 1956

PUBLIC HEALTH SERVICE _ - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 39 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 40 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness 3. Branch of Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA

6. The Histological Investigation of a Case of Retinal Moniliasis
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: The chance finding of a case of retinal moniliasis and the availability of the retina for detailed examination has prompted a thorough study of the histological features. As far as is known, no previous case of monilia infection of the retina has been recorded.

Method Employed: The eyes were obtained at post-mortem some 5 hours following death. They are fixed in formalin, imbedded in paraffin, and then serially sectioned by the investigator so that the small monilia lesion would not be overlooked. Routine histological stains were carried out including the PAS which demonstrated the monilia hyphae within the granulation tissue.

Patient Material: (N-3-517)

		No.	Average Stay - days
Admissions:	Adult Male	-	-
	Adult Female	1	-
	Children Male	-	
	Children Female	-	
Outpatient:	Number of patients:	-	
	Number of visits:	-	

PROJECT DESCRIPTION (Continued)

Major Findings: The lesion in the retina was thought to have had its origin just below the internal limiting membrane, presumably being an embolic infection which had lodged in a small vessel. It had depressed the subjacent retina, considerably thinning out the ganglion cell layer and the internal molecular layer. Exudate had broken through the internal limiting membrane and had spread in the subhyaloid space. Indeed, leucocytes were present over the papilla some distance from the initial infection.

Significance to Neurological Research: Although the case is an isolated one, the fact that it is apparently new to the ophthalmological literature suggested that it was worthy of review and report.

Proposed course of Project: The final observations in this case have been made. Appropriate photographs taken and the paper completed and accepted for publication.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 40 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

BIOLOGIC STANDARDS [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 40 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Septic Retinitis Due to Candida Albicans" to be published in ARCHIVES OF PATHOLOGY (In press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 41 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LAB., BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Human Cortical Physiology
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: To outline the extent and nature of functional representations in the cortex of man.

Methods Employed: 1. Electrical stimulation of the human cortex under local anesthesia during operative exposures.

2. Observation of the apparent effect of selected cortical ablations in man and higher primates.

3. Electrocorticographic recording during stimulation of the exposed human cortex and peripheral recording designed so as to analyze autonomic and motor responses which may follow this stimulation.

4. Electrical stimulation of the cerebral cortex in higher primates under analagous conditions with cortical and peripheral recording.

Patient Material: (N-1-510)

		No.	Average Stay - Days
Admissions:	Adult Male	22	22.66
	Adult Female	12	29.75
	Children Male	4	17.75
	Children Female	3	14.67
Outpatient:	Number of Patients	31	
	Number of Visits	42	

Major Findings: We have continued to record responses from temporal, parietal and occipital cortices. In addition, we have obtained pupillary change and eye movements from the posterior frontal cortex. Likewise, we have obtained sequential responses from the somato-motor and somato-sensory cortices. In these sequences there are responses related to pharynx and larynx. Also, we have tried to evoke similar motor responses under hypothermia without success, despite high voltages. In one case we could not evoke an afterdischarge in posterior frontal cortex under hypothermia. In another patient under hypothermia we evoked a sustained afterdischarge in anterior frontal cortex. This contradiction remains unexplained.

In the laboratory we have mapped the somatomotor cortex of three chimpanzees. In one of these animals we evoked eye movements and pupillary changes from posterior frontal cortex as well.

Significance to the Program of the Institute: Accurate observations of human cortical physiology have a wide clinical and scientific application. The analysis of these observations in terms of "brain maps" has served to integrate the various functions in terms of the entire cortex. Thus, through compilation of brain maps which summarize large numbers of responses, one may obtain ideas as to concentration of function within certain cortical areas.

Proposed Course of Project: We will continue the investigations on effect of electrical stimulation. In particular, we will investigate the effects of hypothermia on this stimulation. These studies will be correlated with similar investigations on chimpanzees.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B. Budget Data

11. NINDB 41 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$7,720	$86,296	$94,016	.34	.66	1.
FY'57					

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
			983
FY'57 (.34)	(.66)	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 41 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Baldwin, M. "The Electrical Stimulation of the Human Temporal Region." Arch. Neurol. & Psychiat. (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 42 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LAB., BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Epileptogenic Mechanisms in the Brain of Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. C. Ajmone-Marsan, M. D., J. M. Van Buren, M. D., D. B. Tower, M. D., I. Klatzo, M. D., and E. J. Laskowski, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: To study causal mechanisms of epileptic seizures in man: a. To study the characteristics of epileptogenic areas in the brain of man.

b. To study the characteristics of the lesions which predispose to epileptogenic changes in the brain of man.

c. To study the clinical expression of these epileptogenic areas in man.

d. To study the electrographic characteristics of epileptogenic activity in the brain of man.

e. To study the approved methods of surgical therapy for these lesions and develop new therapeutic methods.

f. To study brain function as it is exposed in the extravagant experiments devised by these lesions.

Methods Employed:
a. Clinical neurological examination.
b. Special radiographic examination
c. Electrographic examination.
d. Electrocortigraphic examination.
e. Electrical stimulation of the lesion exposed at operation.
f. Selective isolation of the lesion at operation.
g. Cinematographic and sound recording.
h. Histological and chemical examination.

Patient Material: (N-1-511)

		No.	Average stay - days
Admissions:	Adult Male	65	31.17
	Adult Female	51	22.18
	Children Male	11	29.74
	Children Female	11	38.45

Outpatient:	Number of patients:	119
	Number of visits:	174

Major Findings: During the period of this report we have observed patients whose epileptic seizures began in frontal, central, parietal, occipital or temporal regions. Also, we have created epileptogenic lesions in chimpanzees and studied the effects of these lesions under various experimental conditions.

In two cases with active epileptogenic lesions of one or both frontal lobes the inter-ictal behavior was interesting. This was characterized by lack of planned initiative, loss of social inhibitions and apathy. In one of these cases removal of right frontal epileptogenic cortex was followed by a disappearance of this abnormal behavior.

One patient had continuous motor seizures involving face and hand on the left side. This epilepsia partialis continuans disappeared after excision of the right motor cortex representing face, fingers and hand.

Many cases of temporal lobe seizures had bilateral epileptogenic lesions. These cases are usually incapacitated socially and economically by frequent ictal paroxysms and abnormal interictal behavior. One such case came to us after radical excision of the right temporal lobe in another hospital. His seizures and abnormal behavior continued despite the first operation. Therefore, we excised the left temporal lobe so as to include uncus, hippocampus and anterior hippocampal gyrus in the excision. During the subsequent 14 months he has earned his own living and is continuing his education. Obviously he did not have any demonstrable evidence of the Kluver-Bucy syndrome. Similarly, we have excised both temporal lobes in three chimpanzees and followed their course after operation for an average period of 9 months. We did not observe the phenomena described by Kluver and Bucy. It seems clear that radical bilateral temporal excision in man or the chimpanzee does not necessarily cause this complicated clinical condition.

Major Findings (cont'd): Temporal lobe seizures are usually characterized by psychical illusions and hallucinations, whether the origin is unilateral or bilateral. These bizarre psychological changes are crudely analogous to those which follow ingestion of LSD-25 by normal humans. This crude analogy led us to test the effects of LSD-25 on chimpanzees whose temporal lobes had been removed. There is little clinical effect after administration of this drug to animals whose temporal lobes have been removed. There is a striking and obvious effect on normal chimpanzees. The same effect is seen after removal of one temporal lobe. Also, this drug seems to activate epileptogenic lesions (by lead implantation) in the mesial temporal region or in the lateral temporal cortex of chimpanzees. This work may indicate some factual basis for the analogous psychological changes which characterize temporal lobe epilepsy or normal individuals after ingestion of LSD-25.

Lateralization of epileptic discharge in the temporal lobe systems remains a major clinical problem. During the period of this report we have again noted the significance of ipsilateral facial movements as a means of lateralizing the origin of the discharge. In some cases the face moves first on the side of the epileptogenic lesion.

The interictal behavior of patients with temporal lobe epilepsy is also a major problem. One patient with a right temporal lesion was aggressive and violent in the ward environment. During these episodes he repeated one sentence or one phrase monotonously. He was hostile and suspicious on occasion and always quick to take offense. After removal of the affected lobe he became cooperative, friendly, and no longer violent or aggressive. Yet in another patient with bilateral lesions and similar behavior, unilateral excision was not followed by significant psychological changes. There was no improvement whatsoever. Indeed, when the lesions are bilateral, behavior is usually as serious a problem as the habitual seizures. It seldom changes after unilateral excisions.

All psychological changes coincident with epileptogenic lesions are being studied in conjunction with the section on Clinical Psychology.

The specimens derived from temporal lobe excisions are being studied in cooperation with the sections of Neuropathology and Neurochemistry.

Finally, we have begun a system of group observation for seizure patients on the wards and we are continuing their home study in cooperation with the Department of Social Work.

Significance to the Program of the Institute: These observations may contribute towards a further understanding of the psychological mechanisms which seem to find some structural substrate in the temporal lobe. Likewise, we have increased our understanding of surgical therapy in temporal lobe epilepsy.

Proposed Course of Project: We will continue the clinical studies in the operating room and on the ward. With the new organization for seizure observation the ward should provide more data on clinical seizure patterns. In the laboratory we hope to continue the studies of experimental temporal lobe lesions, including the relationship of certain drugs to these lesions.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 42 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
#7,750	$341,056	$348,806	.34	.66	1.
FY'57					

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
			3885
FY'57			
.34	.66	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSIST-ANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 42 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Baldwin, M., Shy, G. M., and Tower, D. B. Chapter on "Cerebral Seizures". PRACTICE OF MEDICINE (Sixth Edition), J. C. Meakins, editor, St. Louis, 1956, The C. V. Mosby Co., p. 1654.

2. Davis, M. M., Jr., and Baldwin, M. "An Intercommunication System for the Surgical Operating Room." 1956 Convention Record (Part 9), Institute of Radio Engineers, P. 24-28.

3. Van Buren, J. M., Baldwin, M., and Alvord, E. A. "The Temporal Horn: Its Development, Normal Variations and Changes Associated with Non-expanding Epileptogenic Lesions of the Temporal Lobe." Acta Radiologica (in press).

4. Baldwin, M., Frost, L. L., and Wood, C. D. "Movements of the Face and Jaw During Epileptiform Discharge in the Temporal Regions." Neurology (in press).

5. Baldwin, M., Lewis, S., and Frost, L. L. "Perceptual Interference After Cerebral Ablation." Neurology (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 43 (C)**
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LAB., BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Hypothermia in Intracranial Surgery
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D., and Kenneth Hall, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives:
1. Observation of human brain under hypothermia.
2. Observation and study of systemic changes related to brain alterations.
3. Observation and study of anesthesia as related to neurological changes.
4. Observation and study of the effects of hypothermia on brain lesions.
5. Experimental correlations in the chimpanzee and other animals.

Methods Employed:
1. Electrical stimulation and electroencephalographic recording.
2. Temperature measurements.
3. Measurement of oxygen saturation of blood.
4. Measurement of acid/base balance of blood.
5. Photography.
6. Clinical observation.

Patient Material:

		No.	Average Stay - Days
Admissions:	Adult Male	1	32.0
	Adult Female	6	14.33
	Children Male		
	Children Female		

(N-11-523)

Major Findings: We have observed the human brain under hypothermic conditions in 36 cases. In all cases, save those with intracranial neoplasm, the brain appears slack and seems to fall away from the overlying dura and skull. In those cases with intracranial neoplasm the brain bulges much as it does at normal temperatures. In all cases the brain was pale, with dark vessels along the surfaces, and in each case the consistency was altered. The cortex and white matter appear tough to the dissecting suction. Vessels bleed sluggishly and the intracranial blood pressure is obviously reduced. This applies to abnormal vessels such as those in arteriovenous malformations.

We have observed the effects of hypothermia on six of these lesions. Also, we noted the gross effects of low temperature in cases with astrocytoma, meningioma, choroid papilloma, metastatic cancer or syringomyelia.

The use of hypothermia in hypophysectomy provided further observations. We noted the effect of cortical stimulation (there was none apparent) and noted spontaneous epileptiform activity in one of these cases. All these patients were debilitated and their postoperative periods were relatively smooth despite this debilitation. Many were poor risks because of cardiac, renal or hepatic deficits. Hypothermia seems to protect these debilitated, deficient patients during major intracranial surgery.

In the laboratory we observed the effect of electrical stimulation and noted the characteristics of electrocorticograms under hypothermia. We did these experiments with chimpanzees. The electrocorticogram is reduced in amplitude, and this reduction is preceded by bursts of slow activity. Electrical stimulation does not excite the motor cortex under hypothermia. Repetitive electrical stimulation of the periamygdaloid region does not produce the seizure activity which always follows this stimulation at normal temperatures. Also, we studied the effect of direct application of cold to the chimpanzee brain when it is hypothermic. It is more difficult to produce lesions by direct application of cold when the brain has been cooled indirectly. With an instrument designed to apply low temperatures directly, we subjected systemic blood vessels to temperatures averaging -120°C. At this temperature the aorta of a cat freezes solid in three seconds. During this time the vessel can be cut at the "frozen" part without bleeding.

We investigated the hematocrit and carbon dioxide combining power of the chimpanzee under hypothermia. The blood is "concentrated" and the carbon dioxide combining power is reduced. Also, we studied cooling methods and the effects of volatile and non-volatile anesthetics on these animals under hypothermia. Comparable studies are being carried on in the human operating room at this time.

Significance to the Program of the Institute: The effects of hypothermia on the brains of higher primates have not been clearly defined. Since the technique of hypothermia is useful in neurological and cardiovascular surgery and is now used extensively, we must acquire information concerning its effects on the brain. Similarly, we must understand the relationship of various anesthetic agents to these cerebral effects. We should also understand the systemic corollaries of the cerebral changes.

These are studies of the effects of low temperature on the human nervous system. Knowledge of these low temperature effects is essential in the solution of certain aviation and military problems.

Proposed Course of Project: This project may be expanded and continued through further observations in the human operating room and the primate laboratory. These observations can be derived by organized study of clinical and experimental material with the techniques of neurosurgery and anesthesiology.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B. Budget Data

11. NINDB 43 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$7,750	5,152	$12,902	.34	.66	1.
FY'57					

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 .34	.66	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 43 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

1. Baldwin, M., Frost, L. L., Wood, C. D., and Lewis, S. "Effect of Hypothermia on Epileptiform Activity in the Primate Temporal Lobe." Science 124: 931 (Nov. 9) 1956.

2. Baldwin, M. "Hypothermic Techniques in Intracranial Surgery." The Montreal General Hospital Reunion Volume, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 44 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LAB., BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Mechanisms of Memory
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence L. Frost, Ph. D., and J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: To further our understanding of those functional representations within the temporal lobe of man and the higher primates which may subserve the mechanisms of memory.

Methods Employed: 1. Electrical stimulation of the human temporal lobe during operative exposure under local anesthesia.
2. Ablation of the temporal areas in higher primates.

Patient Material: (N-1-501)

		No.	Average Stay - Days
Admissions:	Adult Male	22	11.95
	Adult Female	12	11.08
	Children Male	3	16.33
	Children Female	2	7.0
Outpatient:	Number of Patients	29	
	Number of Visits	46	

Major Findings: In three patients we elicited responses which indicate that the neuronal patterns in the temporal lobe may subserve the memory mechanisms. Such responses to electrical stimulation are relatively rare, however. They are commonly encountered only in patients with an epileptogenic lesion in the temporal lobe, and among these only when the activity of this lesion is such as to produce involuntary recollection as part of the habitual seizure pattern.

During the past year we have given some consideration to the relationship of the essential epileptogenic lesion and the spontaneous reproduction of involuntary recollection or memory deficits. Certainly the commonest location for a non-neoplastic epileptogenic lesion is mesial within the temporal lobe. If this is true, it is interesting to conjecture whether a mesial lesion might affect the memory mechanisms more specifically if it was more extensive or if it was located more specifically within the mesial structures. Certainly in our cases the more posterior the extent of the mesial lesion, the more likely that the patient will demonstrate either a deficit of memory or an essential seizure pattern characterized by episodes of involuntary recollection. In the patients which we have studied on the basis of these considerations, it seems clear that memory deficits most often follow lesions which are most posterior as well as most mesial. Furthermore, one can usually predict a difficulty in memory function if the lesions are bilateral and within the mesial structures of each temporal lobe. In three patients we have had occasion to observe significant changes in recollection. Electrographic examination of these patients revealed evidence of bilateral disturbance, and in each case an epileptogenic lesion was disclosed at operation in the mesial aspect of one temporal lobe. It may be that the significant changes in memory mechanisms which follow some temporal lobe lesions are the result of posterior and mesial damage. This damage may be ipsilateral or bilateral. If it is ipsilateral, the deficit in memory mechanisms will be less severe than in those cases with bilateral lesions. Furthermore, an ipsilateral lesion which is active may be followed by severe deficits in recollection, and perhaps this sequence is related to the effect which such a lesion has on the contralateral homologous structures. In one case in which there was evidence of severe memory deficit coincident with bilateral electrographic abnormality, the temporal lobe on the right side was removed.

Major Findings (cont'd): Subsequent to this removal the electrical abnormality on the side opposite to the excision disappeared and, from all practical aspects, so did the memory deficit. The lesion which we removed was posterior as well as mesial within the right temporal lobe.

Obviously memory or recollection cannot be related to one or even more specific structures within the brain so as to exclude all other structures. However, recollection is most frequently disturbed in cases where the mesial temporal region is affected by a chronic lesion. Actually, the longer the duration of the lesion, the greater the effect. This seems to be true in most cases save those whose etiology is characterized by severe destruction of the temporal lobe or by abnormalities of the blood vessels. When the temporal lobe is destroyed, as in abscess, the memory deficit may be severe even though the abscess has acted only over a short period. Likewise, the vascular changes, such as embolic phenomena or atherosclerosis, seem to produce an alteration in memory in a relatively short period, even though one may suspect that these etiological factors had been active for some time before they became apparent to the clinical observer.

In those cases where involuntary recollections are characteristic of the habitual seizure pattern, we have asked the patient to draw a diagram or describe in writing the nature of his recollection. This is asking for a voluntary recollection of a memory pattern not ordinarily available to conscious recall. Whatever the nature of the request, it is in most cases followed by some degree of activation of the clinical seizure pattern. Thus, if the patient is questioned carefully on the nature of the dream or flash of past experience which has come before his consciousness at the times of previous seizures, he is very apt to begin a seizure pattern during the immediate questioning. Interestingly enough, he can diagram or draw the scene of the involuntary recollection as it occurs in the ictal sequence, and at the same time he seems aware of his surroundings and, if questioned concerning the questions after the seizure is over, he will recall the details of this interrogation.

Patients who complain of memory deficits and who also have demonstrable epileptogenic abnormality in one or both temporal lobes usually have some difficulty in estimating time. In some cases they have been aware of this difficulty but in most they are unaware of it. It does not seem to be directly related to the alterations in consciousness which may characterize their seizures and it is usually described as a "forgetting that so much time has passed" or in misjudging the duration of short periods.

In the laboratory we continued our study of the effects of unilateral and bilateral temporal lobe excisions in the chimpanzee. Bilateral excisions do not seem to influence or alter previously learned patterns of activity such as feeding, grooming and role in hierarchy, nor do they seem to influence the response of the animal to humans. These observations are contrary to those of some other

Major Findings (cont'd): investigators; yet they have been consistently obtained over an 18-month period. On the other hand, an epileptogenic lesion in one or both temporal lobes seems to be related to periods in which the animal does not undertake previously learned activities with appropriate skill. This relationship is only evident after several periods in which the lesion has been active. It is not a period of confusion or other postictal disturbance because it is not apparent in the immediate postictal period, and it may continue for 24 or 48 hours after clinical evidence of epileptic discharge has passed.

Significance to the Program of the Institute: This and the allied projects are significant to the Institute because they may provide information concerning the structural basis of mental function.

Proposed Course of Project: It seems profitable to continue the study in the human operating room and in the primate laboratory, as well as on the wards. A steady accumulation of information concerning the results of electrical stimulation, the effect of experimental lesions, and the effect of clinical lesions may be combined so as to provide further conclusions.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 44 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57 $7,750	5,152	$12,902	.34	.66	1.

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 .34	.66	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSIST-ANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 44 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Baldwin, M. "Modifications psychiques survenant apres lobectomie temporale subtotale." Neuro-Chirurgie (Paris) 2: 152-167 (1956).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 45 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness 3. Surgical Neurology
INSTITUTE OR DIVISION LAB., BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders 5.
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. An Investigation of Speech Function Localized in the Temporal Areas of Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence L. Frost, Ph. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: To outline the extent of cortical speech representation in man and to understand the relative significance of the areas outlined in speech functions.

Methods Employed: 1. Electrical stimulation of the temporal and parietal cortex in patients during operations under local anesthesia.
2. Clinical Examination of speech function before and after such operations.

Patient Material: (N-1-508)

		No.	Average Stay - Days
Admissions:	Adult Male	20	13.45
	Adult Female	11	27.82
	Children Male	7	22.29
	Children Female	3	11.33
Outpatient:	Number of Patients	33	
	Number of Visits	44	

Major Findings: We continue the outline of speech representation in the human cortex.

Electrical stimulation of the so-called Broca's convolution usually causes speech arrest. If a stimulus is applied to this area so as to cause arrest of speech, a subsequent stimulus of lower voltage may cause hesitation but not actual arrest. This hesitation sounds like stammering, and the patient usually says that he "stammered" or stuttered. During these stimulations he will find it difficult to use the fingers of his writing hand. However, electrical stimulation of the posterior temporal cortex does not interfere with voluntary manipulation of the writing fingers. The speech arrest which follows stimulation of Broca's area is not coincident with any movement of tongue, nor does the patient become aware of any sensation in his tongue or throat. In the speech arrest which follows stimulation of motor tongue representation, the patient is aware of tongue movement or sensation and he may speak in a slurred fashion.

Speech arrest may also follow establishment of an afterdischarge in the lateral temporal cortex close to the pole. This electrographic seizure is coincident with a type of speech arrest usually associated with posterior temporal lesions. If the lateral temporal cortex is incised (by subpial dissection) along a line just anterior to the vein of Labbe, an afterdischarge in anterolateral cortex will not be coincident with speech arrest. This suggests that aphasia which follows electrographic seizures of the anterolateral temporal cortex may be caused by transcortical spread rather than by indirect propagation from deep nuclei.

As previously noted, individuals with temporal lobe lesions have difficulty in speech regardless of the side of the lesion. When the lesion is in the non-dominant temporal lobe, the speech may be indirect, unnecessarily complex and difficult to analyze for meaning. When lesions occur in both temporal lobes in the same patient, speech is always characterized by dependent clauses, qualifying conjunctions, redundancy and repetition. Simple sentence structure is rare.

Tests of aphasia and verbal and visual abstraction have been used. Aphasic type responses have been obtained in approximately 60% of the cases in which an epileptogenic focus has been found in the left temporal lobe. A preliminary survey indicates that there is a difference between the written and verbal abstractions of

Major Findings (cont'd): patients with intracranial pathology. This has not been qualified nor related to site of lesion.

The abstracting abilities of all patients tested show some degree of concreteness or literalness.

In the laboratory we have begun a study of communication patterns in the chimpanzee. These animals use vocalization as a principal means of communication in feeding, certain play activities, and in response to fearful situations. We have recorded specimens of this type of communication. We will investigate the effect of cortical excisions on its nature and use.

Significance to the Program of the Institute: Speech is among the most complicated functions of the human brain. We know little of its intrinsic mechanisms. Some knowledge of these functions provides great assistance to the neurologist in diagnosis of brain disease and in the rehabilitation of those with brain lesions. This project relates to the one on vestibular and auditory function and also to the psychological study of speech. In combination these projects should provide information of value to the neurologist, psychologist and psychiatrist.

Proposed Course of Project: We will continue along present lines and add more precise methods of testing speech in the operating room as well as methods designed to outline the cortical representations of hearing and vestibular function.

We will continue our laboratory investigation as outlined above.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B. Budget Data

11. NINDB 45 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$7,750	5,152	$12,902	.34	.66	1.

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.34	.66	1.	

FY'57

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 45 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 46 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Activity of Cortical Nerve Cells
PROJECT TITLE

7. Choh-luh Li, M. D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objective: To study the activity of cortical cells in response to the activity of the cortical nuclei.

Methods Employed: To record electrical activity of individual cortical neurones with a micropipette electrode having a diameter of less than half a micron at the tip. The activity was then conditioned by impulses initiated from subcortical nuclei.

Major Findings: It was found that the primary cortical sensory neurones were facilitated by synaptic volleys initiated from the unspecific thalamic nucleus. (2) The activity of the neurones in the motor cortex were found to be inhibited by stimulation of the nucleus ventralis lateralis of the thalamus. (3) The synaptic delay of thalamocortical transmission was found to range between .7 to 1.25 milliseconds.

Significance to Neurological Research: The above observations provide significant information about the integrating mechanism in the function of the cortex and thalamus.

Proposed Course of Project: Further studies are underway to explore the motor function of the cortex with respect to the activity of the motor pathways at a lower level. This includes the cortico-spinal system and the nerve-muscle preparations.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 46 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY '57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 46 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Facilitatory Effect of Stimulation of an Unspecific Thalamic Nucleus on Cortical Sensory Neuronal Responses. J. Physiol. (1956) 131, 115-124.

The Inhibitory Effect of Stimulation of a Thalamic Nucleus on Neuronal Activity in the Motor Cortex. J. Physiol. (1956) 133, 40-53.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 47 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Study of Neuronal Humoral Transmission
PROJECT TITLE

7. Choh-luh Li, M. D.
PRINCIPAL INVESTIGATOR

8. Peter Gouras, M. D., and Roger M. Morrell, M. D.

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objective: To study the change of electrical activity of the brain in an animal, the blood circulation of which was connected with another.

Methods Employed: Cross circulation was established between a donor and recipient cat. The electrical activity of the cortex and the heart were recorded from both animals. Cortical responses of the recipient to stimulation of the donor were studied.

Significant Findings: It was found that the head of the recipient cat completely isolated from its body could be kept alive for several hours at the expense of the circulation of the donor. Similarly, the body of a cat without its head could be kept alive for as long as six hours merely depending upon artificial respiration. This is not surprising in view of the fact that the Russians had once transplanted a dog's head to the body of another dog; however, from our observations stimulation of the reticular formation in the midbrain of the donor failed to "arouse" the cortical activities of the recipient; this is in contrast to the

experiments conducted at Columbia University and suggests that more careful studies should be carried out in order to establish the theory of neuronal humoral transmission.

Significance to Neurological Research: The cross-circulation experiment is vitally important in the study of endocrinology. For example, it has been claimed that the humoral output of the pituitary is utilized by the target organs; thus, in the circulation pituitary concentration is relatively low. If this is true, the preparations described above can settle the argument once and for all. Further, the relation between the activity of the hypothalamus and the pituitary can be quantitatively studied.

Proposed Course of Project: This project will involve investigators who are familiar with protein chemistry and Endocrinology. It is hoped that eventually a profusion apparatus can be developed with which the activity of the brain can be studied in vitro.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 47 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	5,152	$ 12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 47 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 48 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Nerve-Muscle Activity in Reference to Temperature Changes
PROJECT TITLE

7. Choh-luh Li, M. D.
PRINCIPAL INVESTIGATOR

8. Peter Gouras, M. D.
OTHER INVESTIGATOR

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To study the conductivity of the peripheral nerve, the responses of endplate potentials and contactility of muscle fibers in amphibia and mammals.

Methods Employed: The action potentials of the motor nerve were recorded under various control temperatures as indicated by the thermocouple. Likewise, the endplate potentials were recorded subsequent to curarization. The muscle action potentials were subjected to similar investigations. These were carried out under a dissecting microscope with a recording electrode made of platinum wire 12 microns in diameter. The manipulation of the platinum electrodes under the microscope enabled individual fibers to be selected for recording. Twitch-tension and tetanic contractions of the muscle were also studied with a strain gauge.

Major Findings: The observations essentially confirm those previously obtained by Katz, Kuffler & Eccles and Hill. The only contributions which could be claimed from these studies might be that quantitative information was provided. In addition, it was found that the muscle fibers are more readily responsive to cold temperature than the nerve and the endplates.

Significance to Neurological Research: The above observations may bear some importance in muscle metabolism under hypothermia which has become increasingly important in operative procedures.

Proposed Course of the Project: This project is in progress and the definitive conclusions seem to be awaiting further observations obtained by intracellular studies of the nerve action potentials, endplate potentials and muscle action potentials. As soon as the survey studies with extracellular recording electrodes are completed, intracellular studies will begin.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 48 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 48 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 49 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Epileptic Discharge of the Amygdaloid Complex
PROJECT TITLE

7. Choh-luh Li, M. D.
PRINCIPAL INVESTIGATOR

8. Peter Gouras, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To study the discharge initiated in the amygdaloid nucleus in relation to the activity of the subcortical structures.

Method Employed: The amygdaloid nucleus was rendered epileptic by either electrical stimulation or injection of high concentration penicillin solution. The epileptic discharge was recorded from various subcortical structures and its changes were studied by stimulation of other subcortical nuclei.

Major Findings: Latency studies appear to indicate that there are direct pathways between the amygdaloid complex and the temporal cortex. It was found that direct pathways also exist between the amygdala and the medial ventral nucleus of the hypothalamus. Our data also suggests that the discharge of the medial ventral nucleus of the hypothalamus inhibits the epileptic activity. Desynchronization of the epileptic activity recorded from the amygdaloid nucleus was also observed when the reticular formation of the midbrain was activated.

Significance to Neurological Research: Since temporal lobe epilepsy is found to be closely related to the activity of the amygdaloid complex, the understanding of the underlying mechanisms of epileptic discharge in the amygdala will contribute some knowledge to temporal lobe epilepsy. If it is true that activation of the reticular system is capable of suppressing the epileptic discharge initiated in the amygdala, therapeutic measures directed to the activity of the reticular formation may be considered. The preliminary observations may not be definitive, but it will probably open another channel for research in connection with temporal lobe epilepsy.

Proposed Course of Project: This research project will be eventually facilitated by the perfection of remote stimulation and recording research project.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 49 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 49 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 50 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. _____
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Origin of Fibrillation Potentials in Denervated Mammalian Muscle Fibers
PROJECT TITLE

7. Choh-luh Li, M. D.
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: To study the origin of the spontaneous electrical activities in mammalian muscles following denervation.

Methods Employed: The serratus anticus of the guinea pig was chosen for study. The long thoracic nerves were cut under aseptic conditions and the animals kept alive. The spontaneous electrical potentials were recorded at intervals of from 1 to 30 days after the serratus anticus had been deprived of its motor supply. This was carried out with intracellular electrodes which were also capable of delivering stimulating currents; thus, the fibers under study could be activated intracellularly.

Major Findings: At the present time no definitive conclusions can be made; however, there is some indication that the spontaneous action potentials are initiated at the endplate region.

Significance to Neurological Research: This study may provide basic information in connection with the mechanism of neuromuscular transmission and further the understanding of some of the muscular diseases.

Proposed Course of the Project: This study is a continuation of the project investigated with the collaboration of Dr. G. Milton Shy and Mr. Jay Wells. In the future it is hoped that fibrillation potentials in patients with peripheral nerve injuries can be studied intracellularly.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 50 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	5,152	$12,902	.33	.66	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.33	.66	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 50 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. CRP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 51 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. _____
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Remote Stimulation and Recordings of the Electrical Activity of the Nervous System
PROJECT TITLE

7. Choh-luh Li, M. D.
PRINCIPAL INVESTIGATOR

8. George Johnson
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: (1) To study the responses of the monkey by high frequency pulses emitted from a transmitter at a remote distance. (2) To study the spontaneous activity and response to the high frequency pulses at a remote distance through an implanted relay system.

Methods Employed: The stimulating electrodes were implanted in the brain and were connected to a small radio receiver unit. The latter was buried in the abdomen of the monkey. Repetitive square pulses at a frequency of 13.5 megocycles per second were generated by a transmitter having a power of 500 Watts. The high frequency pulses were modulated through a pulse generator. Recording electrodes were implanted in chronic monkeys; the electrodes were connected to a transistor through which the electrical activity was broadcast and registered at a distance.

11. Major Findings: Epileptic seizures could be repeatedly produced according to the methods described above.

Significance to Neurological Research: This research seemed to provide a new method to investigate epilepsy artificially produced in animals. It is also possible to observe the behavior patterns of the animal in response

to stimulation of certain neuronal structures. The remote stimulation seemed to remove those factors such as attention and various degrees of consciousness from the behavior responses evoked by stimulation in the laboratories. Similar significance may be applied in the study of spontaneous electrical activity of the brain which is known to be affected by the conscious state of the subject.

Proposed Course of the Project: This research program has encountered numerous technical difficulties. Up to the present time numerous improvements have been made; however, it is possible that in about six months time the stimulating system can be perfected to an extent that experimental animals can be stimulated at a remote distance as a routine experimental procedure. Once this has been accomplished, remote recordings can be achieved with relative ease.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 51 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 51 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 52 (C)**
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Disorders
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Investigation of Second Sensory Areas in Man
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To outline the extent and nature of these sensory representations in man and if possible discover their functional significance.

Methods Employed:
1. Electrical stimulation of these areas under local anesthesia during operative exposure.
2. Recording of these results.
3. Electrographic recording during these stimulations.

Patient Material: (N-1-505)		No.	Average Stay - days
Admissions:	Adult Male	13	9.15
	Adult Female	5	11.60
	Children Male	3	16.33
	Children Female	2	7.50
Outpatient:	Number of Patients:	25	
	Number of Visits:	31	

Major Findings: We have elicited sensory responses from upper bank of the sylvian fissure or from the lateral temporal cortex in 67 cases. We have recorded 35 such responses from the right or left temporal cortices. Some of these were recorded in cases from which we also elicited a sensory response from the upper bank of the

sylvian fissure. The sensory responses (from temporal cortex) are described as 'tingling'. This usually is felt in upper or lower extremity on the same side as the origin of stimulus. Occasionally the patient feels a tingling in the ipsilateral face. This particular response is similar in location to the sensory effect of periamygdaloid stimulation. It is interesting that these sensory responses from temporal cortex are usually ipsilateral and that they are occasionally associated with a sensation that the affected limb is about to move. Such characteristics are reminiscent of those described in Penfield after stimulation of the upper bank of the fissure of sylvius close to the usual representation for tongue. It seems that the second sensory areas extend over the temporal cortex which is functionally related to the amygdala. Furthermore, some responses from the amygdaloid region are sensory and these are similar to those derived from temporal cortex or the upper edge of the sylvian fissure.

Significance to the Program of the Institute: This project is significant as a step toward further understanding of temporal lobe epilepsy.

Proposed Course of Project: We will continue investigation of these areas in man. In the immediate future we hope to improve the technique of stimulation, test the evoked potentials and add new methods of recording the effects of stimulation.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 52 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57 $7750	21,157	$28,907	.34	.66	1.

BUDGETED POSITIONS			
PROF	OTHER	TOTAL	
			PATIENT DAYS 241

FY '57 .34 .66 1.

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Calendar Year 1956

Form No. ORP-1
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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 52 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

Form No. ORF-1
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(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 53 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. A Histological Study of Papilledema
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: It is the object of this work to further advance knowledge as to the precise changes occurring in the eye in papilledema. Although sporadic papers regarding the cytopathology of papilledema have appeared in the past 50 years, in only one instance (Cone and MacMillan) have attempts been made by the use of specific metallic methods to stain completely the structures undergoing change of papilledema. As far as is known to the author no studies with the Golgi method have been made previously in adult human autopsy material.

Method Employed: It is of primary importance to fix the retina immediately following death. In order to accomplish this, concentrated formalin is injected within the globe at the bedside. By the time the post-mortem examination is undertaken, the retina has been completely fixed and the posterior part of the eye can be removed without damaging the retina. Fixation is then continued in 10% formalin until it is convenient to undertake the Golgi staining. The staining method is a combination of potassium bichromate and potassium acetate mixture in which the eye is incubated at 37 degrees for 10 days to 2 weeks. It is then transferred to a warm 1% silver nitrate solution for 48 hours. The eyes are then rapidly dehydrated in ab-

PROJECT DESCRIPTION (Continued)

solute alcohol and transferred immediately to thin celloidin in which they are kept for 48 hours. Following this they are transferred to thick celloidin for a few minutes, then transferred to a mounting block, thick celloidin poured over the specimen, and the whole specimen and the mounting block immediately immersed in chloroform for hardening. Thus the eyes are not infiltrated but rather included in the celloidin. This inclusion is sufficient to permit sectioning at 100 micron intervals which is needed for this method.

Patient Material: (N-12-516)

		No.	Average stay - days
Admissions:	Adult Male	3	-
	Adult Female	4	
	Children Male	1	
	Children Female	-	

Major Findings: No important observations have been made beyond confirmation of the findings found in the report of December 1955. The histological work, however, on less than half the available material has been finished so much remains to be reviewed.

Significance to Neurological Research: The precise cause and the structural changes of papilledema have not been elucidated to date in the literature so further data is sought.

Proposed course of Project: Collection of material (at present eleven cases of papilledema are available) will be continued as well as further investigation of histological techniques which may serve to better bring out the changes in papilledema.

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(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 53 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	5,152	$12,902	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.66	.99	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 53 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 54 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Branch of Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Neurosurgical Service
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. A Vestibular Representation in the Temporal Lobe
PROJECT TITLE

7. J. M. Van Buren, M. D.
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: This study is undertaken to define the anterior boundary of the nystagmogenic area of the temporal lobe in man. It has been shown since the early portion of the 20th Century that lesions in the hemisphere of man produce accentuation of the quick phrase of caloric nystagmus toward the side of the lesion. It has been subsequently demonstrated by Carmichael and Hallpike that this quick phase predominance toward the side of the lesion occurs whether cold water is irrigated in the contralateral or warm water is irrigated in the ipsilateral ear. The latter authors have further shown that the area responsible for this change lies in the posterior temporal region.

Because of the availability of patients in whom a measured quantity of temporal lobe had been removed for epilepsy, it was decided to follow out these studies to determine the anterior border of the portion of the cerebral cortex which affects the ocular response to caloric stimulation of the ears.

PROJECT DESCRIPTION (Continued)

Method Employed: Prior to temporal lobectomy, a control examination was carried out and the same examination repeated following removal of measured portions of the temporal lobe. This examination consisted in positioning the patient with the neck flexed 30 degrees, and irrigating the external ear canals for 30 seconds with water 7 degrees above and 7 degrees below body temperature. Using a stop watch, the time of regular nystagmus was measured from the time the irrigation of the ear canal was commenced. In this way, a roughly quantitative measurement was obtained, which could be compared in the pre and post-operative periods.

Patient Material: (N-1-502)

		No.	Average Stay - days
Admissions:	Adult Male	11	6.27
	Adult Female	11	6.18
	Children Male	3	17.0
	Children Female	3	3.0
Outpatient:	Number of patients:	10	
	Number of visits:	10	

Major Findings: Although prior to the publishing of the Annual Report in December of 1955, it had appeared that the method employed was capable of producing useful results on careful consideration of the data it became evident that it was of little value. The reason for this lay in the difficulty in estimating by observation the end of nystagmus and thus setting a definite time for quantitative estimate of the duration of nystagmus.

Significance to Neurological Research: The previous studies of nystagmus have been made by the use largely of cerebral tumors or, in a few cases, of large destructive vascular lesions. The final localization of the phenomonen was carried out by the method of super-imposition of the lesions upon a brain chart. The inherent weaknesses of this type of material and the method of examination are apparent. It has therefore been felt of use to review this data using a more precise and quantitative cerebral lesion in man, such as can be obtained after removal of an epileptogenic lesion.

Proposed course of Project: As mentioned above, under the major findings, the use of a method involving simple observation for the timing of nystagmus has been found to be unreliable for quantitative data. Therefore, it is necessary to discard all the work to date using this method.

A new method of attack is planned using EEG recordings of the potentials between electrodes placed on the lateral borders of the orbits. Because of the strong electrical potential, across the eye it may be possible to record satisfactory nystagmograms by this method. If a satisfactory objective measurement of nystagmus cannot be achieved by this method, it will probably be necessary to abandon the project.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 54 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,750	16,855	$ 24,605	.33	.66	.99

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.66	.99	192

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 54 (C)

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 55 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Primate Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. A Study of Functional Representation in the Amygdala of Man and the Higher Primates
PROJECT TITLE

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. Laurence L. Frost, Ph. D., and Shirley Lewis, R. N.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further understanding of the functions and functional connections of this important nucleus in man and the higher primates.

Methods Employed: 1. The electrical stimulation of the amygdaloid nucleus in patients under local anesthesia during operative exposure of the temporal regions.

2. The electrical stimulation of the amygdaloid nucleus in higher primates during operative exposure of the temporal regions and as chronic preparations after implantation of deep electrodes.

3. Electrographic recording from the temporal, parietal, frontal and deep temporal regions during these electrical stimulations.

Patient Material: (N-1-504)		No.	Average Stay - days
Admissions:	Adult Males	15	8.33
	Adult Females	9	13.33
	Children Male	3	16.33
	Children Female	2	7.0
Outpatient:	Number of Patients:	23	
	Number of Visits:	29	

Major Findings: We have stimulated the periamygdaloid region of 15 patients. This electrical stimulation has provided motor, sensory and autonomic responses. As previously reported, the motor responses are movements of the face, jaws and tongue. The face movements are ipsilateral and are usually described as "tingling" in the side of the face or cheek. In some cases the patient thought that the side of his face was moving when no movement was observed. Perhaps these are motor responses to subliminal parameters.

Salivation is a rare response to stimulation of this area in the human. However, it may occur, and its occurrence is characterized by profusion. The patient "feels" the saliva pouring out. This is quite different from the complementary salivation which follows the motor responses. Other autonomic responses are more common. As previously noted these include respiratory arrest and some change in sweating. Recently we have also observed color changes in the face, as well as tachycardia.

In the laboratory we have created epileptogenic lesions in the periamygdaloid region of two chimpanzees. These animals now have seizures characterized by initial face movement. Their attacks begin with pulling of the mouth towards the side of the lesion, followed by chewing, salivation and alteration of consciousness. One animal pulled at his chest with both hands and crawled about the cage in a random fashion. During this period his consciousness was altered and he could not be diverted from his activity. Both animals have begun seizure activity immediately after ingestion of LSD-25. Twice, after administration of this drug, continuing seizures or status developed. In one animal seizures followed intrathecal injection (in Elliott's solution).

Significance to the Program of the Institute: The amygdaloid nucleus is an important structure within the temporal lobe. We are studying temporal lobe epilepsy in this Institute. Certainly these studies require more information concerning the basic functions of important temporal lobe structures such as the amygdaloid nucleus.

Proposed Course of Project: We will continue the clinical and laboratory studies. More precise stimulation techniques may yield more useful information.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 55 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	26,249	$ 33,999	.34	.66	1.

BUDGETED POSITIONS			
	PROF	OTHER	TOTAL
FY '57	.34	.66	1.

PATIENT DAYS 299

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 55 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Baldwin, M., Frost, L. L., and Wood, C. D. Investigation of the Primate Amygdala: Movements of the Face and Jaws: II. Effect of Selective Cortical Ablation." Neurology 6: 288-293 (Apr)56.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 56 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness

2. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Primate Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. An Investigation of the Autonomic Phenomena which Follow Stimulation of the Temporal Areas in Man and Higher Primates

7. Maitland Baldwin, M. D.
PRINCIPAL INVESTIGATOR

8. J. M. Van Buren, M. D., Laurence L. Frost, Ph.D., Shirley Lewis, R.N.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION

Objectives: To further understanding of the central representations of autonomic function.

Methods Employed: 1. Electrical stimulation at operation.
2. Electrographic and electronic recording during this stimulation.

Patient Material: (N-1-506)

		No.	Average Stay - days
Admissions:	Adult Males	17	8.71
	Adult Females	4	4.50
	Children Male	3	16.33
	Children Female	1	7.0
Outpatient:	Number of Patients:	25	
	Number of Visits	31	

Major Findings: It seems clear that electrical stimulation of the insular cortex or amygdaloid nucleus is followed by autonomic changes. As previously noted, these consist of alterations in gastric motility, blood pressure, pulse, and respiration. Also it seems that stimulation of the periamygdaloid region in humans is frequently followed by pallor, flushing, or sweating.

In some patients we have reproduced an epigastric sensation by stimulation of the periamygdaloid region. Certainly such a sensation can be associated with epileptogenic discharge in the

mesial temporal regions. It may also be coincident with alteration in pulse rate (tachycardia), inspiratory arrest, increase of gastric motility and changes in the color and temperature of the skin, as well as pupillary dilatation. The human patient associates the subjective appreciation of these changes with a feeling of fear. We have noted the objective concomitants of this feeling during stimulation of the uncus and amygdaloid region.

Significance to the Program of the Institute: These are observations on the cerebral representations of autonomic function. They are relevant to the physiological substratum of most temporal lobe seizures.

Proposed Course of Project: We will acquire a polygraphic instrument with which we can record evidence of the various objective changes. This simultaneous recording may provide a quantitative estimate of the various alterations as they relate to location and type of stimulus.

Form No. ORP-1
October 1956
(Attachment I)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 56 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,750	$20,016	$27,766	.34	.66	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.34	.66	1.	228

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB 56 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A: Project Description Sheet 1. NINDB 57 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness 3. Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPT.

4. Clinical Neuropathology 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Study of the Blood-Brain-Barrier in Brain Injury Produced by Cold.
PROJECT TITLE

7. Igor Klatzo M.D.
PRINCIPAL INVESTIGATOR

8. E. J. Laskowski M.D. & A. Piraux M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

GENERAL STATEMENT:

The question of brain edema is of paramount importance to the neurosurgeon as a main complication in cases of brain injury. There is no question that one of the major factors in the development of brain edema due to injury is the increased permeability of the blood-brain-barrier (B.B.B.).

Many aspects of this problem still remain obscure. There is little information available concerning time of onset, rate and topography of spread, involvement of distant areas such as brain stem etc. Morever, many of the previous investigations on experimental brain injury and edema are subject to criticism on two main points:

1) The experimental technics for production of brain injury have been rather crude and the intensity of injury varied from animal to animal.

2) Only histological technics have been used in studies of morphological changes. It is true that the histological artefacts produced by different factors, i.e. fixation, embedding etc. are nototious for imitating various appearances described by a number of authors as characteristic of brain edema.

In order to avoid or miminize the objections mentioned above a comprehensive study concerning problems of injury and edema would require:

1) Application of a method in which experimental brain injury can be uniformly reproduced.

2) Application of a method for precise and reliable evaluation of the B.B.B. as a sensitive indicator of one of the major changes leading to brain edema.

The technic of cold injury and fluorescein technic for study of the behaviour of B.B.B. seem to satisfy these two requirements and with their predominant use the following aspects will be studied:

1) Reconstruction of the dynamics of brain edema due to injury by study of different chronological stages of development.

2) Study of effects of varying intensities of injury with particular reference to involvement of distant structures such as brain-stem in an acute, severe injury.

3) Relationship between temperature changes at different depths of the cortex and underlying structures and morphological changes produced by application of cold.

METHODOLOGY:

Technic for production of injury by application of cold has been described in our Project # 513-B. In cats under anaesthesia direct or indirect (through overlying meninges and bone) brain injury will be produced by application of cold metal plate at ($-30^{\circ}C$). Simultaneous measurements of temperature will be carried out by micro-thermocouple introduced to the different depths of cortex and underlying structures.

Intravital use of fluorescein is a method of choice for study of B.B.B. in our project. The lack of toxicity, simplicity of application, and satisfactory visual demonstration in ultra violet light are the main advantages of this method. The most desirable feature, with respect to our particular problem, however, is the possibility of the assessment of the permeability of B.B.B. in ultra violet light in the same block of tissue, which subsequently, can be submitted to further histological and histochemical investigations.

PROGRESS AND STATUS:

Several cats were operated upon to assess the effect of cortical exposure alone regarding changes in B.B.B. A circular opening of 1.5 cm. in diameter was made in the skull and dura was reflected. After one hour of exposure, without drying, the dura was sutured and the overlying structures approximated and closed. Studies with fluorescein and histological control stains revealed no changes resulting from exposure alone. Groups of dogs and cats are submitted now to brain injury by application of cold and the outlined above investigations are in progress.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 57 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$10,500	5,152	$15,652	.5	1.	1.5

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.5	1.	1.5	

FY'57

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 57 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A: Project Description Sheet 1. NINDB 58 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness 3. Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPT.

4. Clinical Neuropathology 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Studies on Localization of Muscle Proteins
PROJECT TITLE

7. Igor Klatzo, M.D.
PRINCIPAL INVESTIGATOR

8. Milton G. Shy, M.D., Beni Horvath & Emily Emmart M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: (N-2-401)

GENERAL STATEMENT:

The Coon's fluorescein isocyanate technic for detection and localization of antigen and antibodies in tissue sections has been successfully used for a great variety of problems. Theoretically, any substance capable of inducing antibody response can be studies by this method.

Myosin, one of the basic protein constituents of the muscle, is presumably antigenic. Repeated injections of myosin into rabbit should induce anti-myosin antibody production. The antibody response might be further enhanced by injection of myosin precipitated on alum phosphate.

The globulin fraction containing anti-myosin antibodies will be isolated from the rabbit's serum and the antibody titers will be determined. These antibodies will be then labelled with fluorescein isocyanate without loss of their specificity.

Fresh muscle preparations, obtained from the biopsies of normal controls and from patients with neuromuscular diseases will be studied. After observations in phase-optics muscle fibers will be incubated with labelled antibody solution. Consequently, the

site of antigen (myosin) - antibody (anti-myosin) reaction i.e. localization of antigen will be studied microscopically in ultra violet light.

It is hoped that this procedure will bring out the fine details concerning the distribution of myosin in a muscle fiber and also provide some information about the behaviour of myosin in various neuromuscular diseases.

Similar studies will be undertaken using other, related to myosin muscle proteins.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 58 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$10,500	5,152	$ 15,652	.5	1.	1.5

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH ☒
REVIEW & APPROVAL ☐
BIOLOGIC STANDARDS ☐
ADMINISTRATION ☐
PROFESSIONAL & TECHNICAL ASSISTANCE ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 58 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A: Project Description Sheet. 1. NINDB 59 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness 3. Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPT.

4. Clinical Neuropathology 5.
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Special Pathology of Epileptogenic Tissue (A) Histochemical and
PROJECT TITLE

Histological Investigations of Human Epileptogenic Tissue.

7. John Van Buren M.D.
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin M.D. & Igor Klatzo M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: (NINDB Project # 513-A)

GENERAL STATEMENT:

The relationship between epileptic activity and structural change in the brain might be a key problem to the understanding of epilepsy itself. The availability of a considerable quantity of epileptogenic brain tissue removed in operation has formed a unique opportunity for the study of this subject.

METHOD EMPLOYED:

The epileptogenic tissue has been divided into two portions. One has been placed for imbedding in paraffin. This allows chromatic stains such as the trichrome and phosphotungstic acid hematoxylin stain, retieulin stain and the hematoxylin eosin. The other portion has been set aside in formal-ammonium bromide. This fragment can be used for metallic stains for the outlining of glia and neurons. Fat and lipid stains can also be carried out on this material. In addition, histochemical technics described in Project B, will be applied. Histochemical data obtained from Project B will be used as a base-line for interpretation of the results in the human material.

PATIENT MATERIAL:

		No.	Average Stay - days
Admissions:	Adult Male	16	9.12
	Adult Female	21	8.29
	Children Male	6	18.83
	Children Female	5	9.4

Outpatient: Number of patients: - (N-1-513)
Number of visits:

MAJOR FINDINGS:

The complete review of the available material has not been finished. Initial findings include the following types of lesions: (1) Pseudolaminar necrosis. This lesion consists of loss of cerebral substance including neurons and glia, limited largely to the central layers of the cerebral cortex. In this area the cerebral substance appears spongy, and is frequently completely destroyed. Lesser changes consist in a loss of neurons in this area. This change is apparently secondary to interference with the fine penetrating blood vessels from the surface of the cerebral cortex. Collateral Golgi stains of cerebral cortex to show the endothelium of the capillaries demonstrates that the maximum density of the capillary network lies in these central layers of the cortex, probably in layer III to upper V. From this, the inference perhaps follows that this area of the cerebral cortex requires the greatest blood supply. It has also been shown by other work that in the lower portion of the cortex a junction is made between the blood supply from the surface and from the white substance. Hence, it is apparent why this area of cerebral cortex is the most vulnerable to mild anoxia. (2) Complete cortical necrosis. This lesion is apparently a continuation of the above-mentioned process in which none of the cerebral cortex remains. (3) Fats and lipid deposition. In many epileptogenic lesions in which there is lack of severe pathological change phagocytes filled with lipid which will stain with sudan IV as well as scharlach have been found in the perivascular spaces and as well at times free in the cerebral substance apparently at a distance from vessels. The origin of this lipid is obscure as in some cases there is no obvious break-down of myelin in tissue. (4) Neuron damage. Damage to the neurons has appeared in many of the sections. The most common change is that of the dense pyknosis of the cell, shrinkage of the cell in decreasing its lateral dimensions and tortuosity of the apical dendrite. It is considered that in many instances this is a traumatic artefact since there frequently is no surrounding increase in the pericellular satelites. A similar change has been shown in a recent paper by Cecile Vogt, published in the Annals of the First

International Congress of Neuropathology. (5) Fibrous astrocytosis of the cortex. In this change, best demonstrated on the metallic impregnations, fibrous astrocytes appear in layers of the cortex in which they are normally absent. They are normally present, of course, in the molecular layer, and occasionally in the VIth layer of the cortex. (6) The meningo-cerebral cicatrix. This is the classical brain scar in which there is a union of the fibrous tissue elements of the dura with the fibrous framework of the cerebral cortex itself, namely, the tissue about the blood vessels. There is general hypertrophy of these structures, a fibrillary astrocytosis and loss of fine capillary supply to the affected cerebral cortex. Or, there may be a considerable quantity of debris arising from myelin destruction, and old blood pigment which is deposited in the phagocytes.

Significance to Neurological Research: Although the basis of epilepsy as yet remains obscure, basic studies on the structural changes of epileptic lesions are necessary for an illucidation of its mechanism.

Proposed course of the Project: It is hoped by further study in this direction, particularly with cytochemical methods, that further knowledge of basic importance may be uncovered in this direction.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 59 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	41,348	#	41,348			

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				471

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publication 15. NINDB 59 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A: Project Description Sheet 1. NINDB 60 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness 3. Surgical Neurology
INSTITUTE OR DIVIDION LABORATORY, BRANCH OR DEPT.

4. Clinical Neuropathology 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Special Pathology of Epileptogenic Tissue (B) Histochemical
PROJECT TITLE

Studies in Experimental Epilepsy

7. Igor Klatzo, M.D.
PRINCIPAL INVESTIGATOR

8. E. J. Laskowski, M.D. & A. Piraux, M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: (NINDB Project # 513-B) (N-1-513)

GENERAL STATEMENT:

The studies on experimental epilepsy are not new; however, our knowledge about the morphological changes is lagging far behind the progress made in evaluation of physiological data from these studies:

The following reasons may account for this:

a) The methods used for production of epileptic seizures involved usually, either a crude injury to the brain (by trauma, electrocoagulation etc.), or introduction of foreign chemical agents. Even in electrically induced seizures various drugs have been given concomitantly. In all these instances there is the basic difficulty of differentiation between effect of an introduced injury (chemical or traumatic) and effect of seizures alone.

b) The methods which have been used for study of the material from the experimental epilepsy were limited mostly to routine neurohistological technics, which may not be sufficiently sensitive to reveal finer changes in the cells as based on the altered metabolism.

To surmount these two inadequacies in the study of experimental epilepsy it seemed appropriate:

a) To apply a method for production of seizures which will avoid traumatic injury or introduction of foreign chemical substances.

b) To use modern, predominantly histochemical technics which may detect early alterations in elements which are of special interest in the problem of epilepsy. These elements include: neurons, ground substance and blood-brain-barrier.

With application of an appropriate technic for induction of the epileptic seizures which would meet the criteria mentioned under a) several groups of animals can be studied: 1) those with frequent and numerous seizures - analogous to epileptic status, 2) chronic group - in which animals would be submitted - to one seizure a day for several months, 3) intermediate group - where animals will have several seizures a day for a certain period of time. Brain tissue obtained from these animals together with a normal control group will be submitted to investigations as mentioned above under b).

With the base-line established from these studies the problem of the relationship between trauma and epileptic seizures can be then approached.

Using application of cold as the most suitable technic for the production of brain injury which can be controlled in extent, the following evaluations will be attempted:

1) Comparison of frequency and severity of seizures between a group of epileptic animals which was exposed to previous brain injury and a group which underwent the same number of seizures but was not exposed to any brain injury.

2) Comparison of morphological features of brain injury produced by cold alone and brain injury in animals which in addition were submitted to numerous epileptic seizures. This comparative study may have bearing on Penfield's theory that the lesions responsible for epileptic seizures have a tendency to selfpropagation.

METHODOLOGY:

The audiogenic stimulation technic seems to meet requirements of our problem. In susceptible strains of mice or rats epileptic seizures can be produced by audiogenic stimulation applying shrill sounds; i.e. door-bell, Galton whistle, or pure tones of proper frequency and sufficient intensity. There is no introduction of any foreign substance and no gross injury to the brain is involved. This technique has been successfully used for psychological studies in mice and rats and also for testing the anti-convulsant drugs. As the refractive period lasts only about 15 minutes there is no problem of dosing the intended number of seizures.

The histochemical methods were selected primarily on the basis of their applicability for the study of important chemical components of those C.N.S. elements which may have special bearing on the problem of epilepsy.

The following histochemical technics will be used:

1) Einarson's gallocyanin method for nucleic acids. This will be combined with quantitative photometric absorption studies in the visible wave range.

2) Enzymatic assay using: acid phosphatase, alkaline phosphatase, naphtol AS esterase, cholinesterases etc.

3) Ground substance studies using Hess' PAS technique.

The behaviour of B.B.B. will be studied by fluorescein, Trypan blue and Trypan red technics. The problem of vasoconstriction versus vasodilatation will be approached by benzidine and other related technics.

All material will be submitted to the Parallel control investigations using the routine neurohistological technics i.e. silver stains, gold impregnation, cresyl violet etc.

For the method of production of controlled injury to the brain the appropriate instrument has been constructed. This instrument consists of a metal plate 10 x 4 mm. which is connected by a metal arm to a glass container which can be filled with dry ice - acetone or any other cold mixtures. The thermocouple gives the temperature readings from the surface of the plate. The surface of the metal plate is modelled according to the curvature of the brain surface. Cold injury can be produced by a) direct contact between pial surface and cold metal plate or by b) application of the metal plate to the skull after reflecting the skin. Operative injury to the brain in this case is completely avoided.

By adjusting the head of the animal (with craniotomy opening or with only reflected skin) to the metal plate with the known standard temperature (-30°C) the amount of the cold applied will be regulated by the time of contact between the plate and the underlying structures. In the present studies on experimental epilepsy in rats only the application of closed cold injury (through the reflected skin) has been considered. EEG studies will be done on the same animals from different groups.

PROGRESS AND STATUS:

For the audiogenic stimulation the sound-proof box with the included door-bell and timer has been constructed. Forty rats of M 520 strain were selected on the basis of successful inducement of epileptic seizures after the first stimulation. All these forty rats have now been submitted to audiogenic stimulation once a day. New groups of selected rats have been started on several audiogenic stimulations per day. The instrument for the production of cold injury mentioned above has been devised and obtained. One group of rats underwent a closed cold injury (10seconds at -37°C), which the animals sustained well. This group and a similar control group without cold injury are submitted to several audiogenic stimulations per day. Histochemical technics mentioned in methodology are being tested for reliability and constancy of the results.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 60 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$16,200	5,152	$21,352	.5	2	2.5

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.5	2	2.5	

FY'57

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSIST-ANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publication 15. NINDB 60 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A: Project Description Sheet 1. NINDB 61 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness 3. Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPT.

4. Clinical Neuropathology 5.
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Special Pathology of Epileptogenic Tissue (C) Tissue culture studies
PROJECT TITLE

7. Igor Klatzo M.D.
PRINCIPAL INVESTIGATOR

8. Choh-Luh Li M.D.
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION: (NINDB Project # 513-C) (N-1-513)

GENERAL STATEMENT:

As a supplement to histological, histochemical, and physiological studies concerning the experimental and human epilepsy a new approach using the tissue culture is considered. The growth of nervous tissue in vivo has been successfully carried out and studied by numerous investigators and the technics involved are well established. With regards to epilepsy the following problems seem to be accessible by the tissue culture method.

1) Study of electrical excitability and conduction in vivo in a single cell isolated in tissue culture under the visual control in phase-optics and using micro-manipulator device for measurements of electrical potential.

2) Testing effects of various convulsant agents on the electrical behaviour of the isolated nerve cells in tissue culture under the visual control of phase optics.

3) Cytological analysis of nervous tissue elements cultured from epileptogenic human foci.

METHODOLOGY:

It is necessary to establish a facility for tissue culture. This would be geared on culturing of relatively small amount of tissue derived from human surgical material and experimental animals. Roller-tube technic appears to be the most suitable for culturing the nervous tissue. Observations will be carried out primarily in phase optics and in time-lapse cinemicrophotography. The micromanipulator and technic for measuring electrical potentials from a single nerve cell has been developed by Dr. Li and will be adapted to tissue culture studies.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 61 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$10,500	5,152	$15,652	.5	1.	1.5

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.5	1.	1.5	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 61 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 62 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Investigation of the Site and the Extent of Lesions Involving CNS in Cerebral Palsy and Allied Conditions.
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To correlate the clinical picture of the patient with the state of brain as seen in pneumoencephalogram. To obtain some insight into the possible etiology and pathogenesis of the encountered lesions, at least in a proportion of instances.

Methods Employed:

1. Genetic investigation.
2. Detailed neurological examination, including psychological testing and EEG.
3. Pneumoencephalogram.
4. Other special tests as indicated.

Patient Material:

		No.	Average Stay in Days
Admissions:	Children Male	21	21
	Children Female	16	18
	Adults Male	5	16
	Adults Female	1	21

Clinical Project N-9-602 and N-9-803

Major Findings:

Analysis of the 43 investigated patients:

Pneumoencephalographic studies contributed considerably to the estimation of the location and extent of the lesion and so aided in the evaluation of the causal origin of the condition. Out of 35 patients who had pneumoencephalograms done, 12 showed the ventricular system and subarachnoid space to be within normal limits thus excluding gross focal damage to the brain. Twenty-three patients had grossly abnormal pneumoencephalograms. Two of them showed evidence of arrhinencephaly - an abnormal development of the brain which must originate before the 28th day of gestation. Two patients showed unilateral porencephaly, thus indicating that a massive focal destruction of the brain had occurred either in the form of infarction or hemorrhage. Three patients had arrested communicating hydrocephalus. Sixteen patients had moderate to marked dilatation of the ventricular system; of these, in seven the ventricular system on one side was more enlarged than on the other; in the remaining nine the ventricular system was abnormally but about symmetrically dilated suggesting a type of pathological process which led to uniform involvement of both hemispheres.

Clinical examination including evaluation of family and personal history helped in formulating classification of the condition in 18 out of 43 patients.

Special tests such as neutralization of virus antibodies, tests for toxoplasmosis, glucose tolerance test, estimation of the CSF neuraminic acid and alike were performed on the material derived from patients and at times also from the mother. In six instances one or other of these tests were helpful in indicating causative factor.

When data derived from all the employed methods of investigation were considered it was found that in 11 out of 43 patients the etiology or precise pathology of abnormal neurological status was established. In 11 of the remaining 32 patients the etiological impression was strongly probable, in 12 possible and in nine the etiology remained unknown. The symptomatic diagnosis was made in all instances.

Significance to Neurological Research: In a majority of cases the etiology of cerebral palsy and allied conditions is poorly understood. Better knowledge of hereditary background, clinical manifestations, as well as the location and extent of the lesion may further our insight into the diverse etiology of these conditions.

Proposed Course of the Project: Further accumulation of data is needed before global analysis can be attempted. However, various interesting aspects arising from the already present material are being elaborated for the purpose of several publications.

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 62 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	~~$11,500~~ $72,864		~~$77,364~~	.34		.34

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.34		.34	830

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 62 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Baldwin, M. Chapter on "Congenital Lesions of the Central Nervous System". Practice of Medicine (6th Edition), J.C. Meakins, editor, St. Louis, 1956, The C. V. Mosby Co., Page 1764.

Dekaban, A.S. Recessive inheritance of mental deficiency - the paper mailed to Arch. Neurol. & Psychiat.

Dekaban, A.S. and Magee, K. Neurological abnormalities in infants born of diabetic mothers. Pending.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Dr. Anatole S. Dekaban has been re-appointed as Assistant Professor of Neurology at the George Washington University Medical School.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 63 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Maternal Condition During Pregnancy and the Course of Birth in Relation to Neurological Abnormalities in the Infants.
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8. Dr. T. E. Cone and Dr. H. H. Hill, Naval Medical Center
Dr. L. J. Geppert and Dr. H. L. Riva, Walter Reed Army Hospital
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: Analysis of various factors occurring in pregnant mothers or complications of birth which may cause or contribute to neurological abnormalities in infants.

Methods Employed:

1. Prenatal care of mothers under research and their individual final assessment.
2. Recording and evaluating of the course of birth and pertinent abnormalities.
3. Examination of the newborn infants during initial hospital stay.
4. Follow-up examination of infants.

Patients Material: Since the Spring of 1956, all deliveries of pregnant women at the Naval Medical Center and Walter Reed Army Hospital as well as the infants born in these two institutions are the subject of this study. (N-9-803)

Clinical Project

Major Findings: A number of abnormalities of the CNS in newborn infants were encountered, examined and recorded. This, however, cannot be evaluated until the project will be in operation at least for one year. Follow-up examinations will begin within the next 2 months.

Significance to Neurological Research: It is known in general that various environmental factors acting during prenatal, intranatal and early postnatal life may be responsible for brain damage and the associated clinical sequelae in infants. This study may be able to reveal the relative importance of certain factors over the others and also their incidence. Since careful and uniform examinations are being conducted during all stages of prenatal and postnatal life, final analysis of the findings may be significant.

Proposed Course of the Project: The outlined examinations and recordings of the data have to continue before the analysis can be attempted. The large and incessant number of subjects under study imposes a particularly heavy load of work on the staff members of this section. This is the more so after an especially trained technical assistant was drafted into the the Army in the middle of our work.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 63 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	0					0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 63 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956.

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 64 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Experimental Production of Congenital Malformations of the CNS.
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8. Marie J. Kendall, B.A.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: The purpose of this project is the production and analysis of congenital abnormalities of the CNS in mice.

Methods Employed: X-ray radiation of mice during different stages of pregnancy.

1. X-ray radiation of pregnant mice from a strain which does not show any significant incidence of spontaneously occurring abnormality of the CNS.

2. X-ray radiation of pregnant mice in stages of pregnancy parallel to the mice in One (1); the strain used here show an abnormally high incidence of spontaneous malformations of the CNS.

3. Gross, skeletal, and microscopic examination of the obtained specimen.

Material: Mice strain: NIH stock "general purpose Swiss Albino" and Black C 57.

Clinical Project

Major Findings: We are considerably limited in space for maintenance of mice. Since only certain age mice can be used, we have to harbour them until they attain it. Then, only about 20 per cent of those kept become pregnant as a result of restricted duration of mating time. In strain "general purpose Swiss Albino" 47 litters were obtained from irradiated mothers. Approximately 1/6 of these had major abnormality, approximately 1/4 moderate to mild and the remainder are free from detectable abnormalities. In strain Black C 57 only four litters were obtained from irradiated pregnant mothers up to date.

Significance to Neurological Research: Morphogenetic and pathological analysis of congenital abnormalities of the CNS at different stages of development will be utilized as an adjunct in explaining similar abnormalities occurring in humans.

Proposed Course of the Project: Accumulation of more material in both strains of mice is needed before attempting an analysis. This will continue during the next year.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 64 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$22,000	5,151	$27,151	.33	2.	2.33

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.33	2.	2.33	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 64 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 65 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Preparation of the Horizons of the Normal Development of the Major Structures of the CNS in Mice.
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8. Marie J. Kendall, B.A.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: The main purpose of this work is to supply norms of the gross and microscopic structure of the CNS of mice during progressive stages of prenatal and postnatal development.

Methods Employed:

1. Dissection of the CNS of mice of 16 progressive developmental stages.

2. Preparation and staining of serial sections.

3. Identification and outlining of main structures on the low power microphotographs.

Mice Material:

	No. of Horizons Prepared
Stock colony of white albino mice	6

Clinical Project

Major Findings: Careful dissection of brain and brain stem of fetus and young mice in six age horizons were performed. The specimens are sectioned serially and stained. In addition, gross characteristics of ten adult mice brains were studied and measurements statistically evaluated.

Since this is a descriptive anatomical study, the provision of all required horizons must preceed the analysis and outlying of structures. It needs to be stressed that to obtain one perfect set of serial sections for one horizon it is usually necessary to process and section six to 12 brains. Only those sets which are in ideal conditions can be utilized for description and photography.

Significance of Neurological Research: An experimental approach to congenital malformations of the CNS is necessary to help understand certain obscure malformations occurring in humans. The provision of norms of the central nervous system has to preceed the experimental production of congenital malformations, as there does not exist any proper guide in the form of an atlas or of a satisfactory reference during consecutive stages of the development of the mouse.

Proposed Course of the Project: Processing of further age horizons must continue and will require further one to two years of work.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 65 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,000	5,151	$19,151	.33	1.	1.33

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	1.	1.33	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 65 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 66 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Pathological Study of Microgyria
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8. Possibly
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To further the understanding of morphology, pathogenesis and etiology of microgyria.

Methods Employed:

1. Review of the development of the human cerebral cortex utilizing brains of human embryos.

2. Gross and microscopic study of microgyria in pathological specimens.

3. Analysis of the clinical history.

Material:

1. Collection of human embryo brains at representative stages of development and processing of microscopic sections. Stages available at present -- 4.

2. Collection of brains with microgyria for histological processing. Three such brains are being prepared for staining.

Clinical Project (N-9-803)

Major Findings: This project has just begun.

Proposed Course of the Project: To continue collection and processing of pathological specimen.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 66 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 66 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 67 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Measurements of External and Internal Orbital Distance as well as Inter-Pupillary Distance in Children up to 6 Years of Age.
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8. Charles Mullins.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: It has been found that the measurement of the interpupillary distance in humans for the purpose of estimation of abnormality of the sphenoid bone is unsatisfactory. It is thought that either external or internal orbital distance or index thereof should take place of the measurements of the interpupillary distance.

Methods Employed:

1. Measurements of the above-named distances in children at progressive ages beginning from zero to six years of age.

2. Correlation of physical measurements of a small group of children with measurements made on cephalometric x-rays.

3. Statistical analysis in various age horizons.

Children's Material: Measurements of about 25 boys and 25 girls are needed for each age horizon. Up to the present time over 300 measurements have been taken.

Clinical Project (N-9-803)

Major Findings: This project is in its beginning and no analysis of data can be made until sufficient number of measurements are available.

Significance to Neurological Research: To make the estimation of conditions such as hypertelorism more scientific, the measurements of stable bony structures rather than movable organ as eyeball, should be performed. As an example a concommitant divergent strabismus can be given; in this instance measurement of the interpupillary distance for the estimation of the abnormality of the sphenoid bone would obviously give false results.

Proposed Course of the Project: First, sufficient numbers of measurements for each horizon have to be taken. Then, those will be evaluated and standard deviations estimated.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB ~~66~~ 67 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF THE COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB ~~66~~ 67 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 68 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Developmental Neurology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Pathological Studies of the Aborted Embryos.
PROJECT TITLE

7. Anatole S. Dekaban, M.D.
PRINCIPAL INVESTIGATOR

8. Dr. H. H. Hill and Dr. H. L. Riva
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION: **(N-9-803)**

Objectives: Attempt to correlate encountered abnormalities in embryos, placenta and umbilical cord on the one hand with clinical deviations of maternal state during the pregnancy.

Methods Employed:

1. In cooperation with Gynecology services of the Naval Medical Center and Walter Reed Army Hospital clinical evaluation of maternal conditions prior to abortion is carried out.

2. Gross examination of aborted products.

3. Microscopic examination of aborted products with special emphasis on Central Nervous System, placenta and umbilical cord.

Material: Products of abortion. Medical records related to respective abortion.

Major Findings: Up to date 31 embryos were examined and in a few instances a significant pathology was encountered. However, this is the beginning of the study and no involved evaluation is as yet possible.

Significance to Neurological Research: This study is of special importance and is complimentary to the parallel studies on neurological abnormalities in surviving infants described under Project No. NINDB 63 (C).

Proposed Course of the Project: This project began several months ago. Further accumulation, processing and evaluation of the material must continue before analysis can be made.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 68 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 68 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 69 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Psychology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Function of the Temporal Lobe in the Recording of Experiences.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, Mildred Blevins
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To investigate the role of the temporal lobe with its structures and central connections in learning, recollection, recall, and reproduction of learned material.

Methods Employed: (a) Psychological tests and more specific tests to measure learning are administered to patients with cerebral seizures. In patients receiving surgical therapy for their seizures, these tests are readministered post-operatively. (b) Observation of chimpanzees before and following surgical removal of cerebral tissue.

Patient Material: (N-1-301)

		No.	Average Stay - days
Inpatient:	Adult Male	25	
	Adult Female	23	
	Child Male	0	
	Child Female	0	
Outpatient:	Number of patients	14	
	Number of visits	14	

Major Findings: (a) 1. Patients with epileptogenic foci in the temporal lobe of the dominant hemisphere are less adept in verbal skills than patients with epileptogenic foci in the temporal lobe of the non-dominant hemisphere. This relative impairment of verbal skills in one group of patients may render them more prone to learning difficulty in verbal material. "Tactual-kinesthetic" learning apparently is acquired relatively slowly in most patients with intracranial pathology. Early findings suggest that learning of this sort is acquired more slowly in patients with epileptogenic foci in the non-dominant hemisphere.

2. Many of these patients with intracerebral pathology do not attend or concentrate well particularly on materials which lack meaning appropriate to the patient. Such material is represented by mental arithmetic or digit-symbol substitution. If the patient is presented with material into which he can read personal meaning or if the stimuli to learning have been forceful enough, recall of the material has been adequate.

3. Immediate, recent, and remote memory of a routine and impersonal nature has been demonstrated to be not at wide variance from that obtained from "control" groups of subjects. Personal memories of recent and remote temporal qualities are yet to be studied.

(b) Observation of chimpanzees has shown that removal of one or both temporal lobes does not markedly alter their behaviour in old learning (habits of feeding, etc.) and does not appear to change their recognition of cage mates or of personnel handling them.

Significance to the Program of the Institute: Patients with chronic or acute intracerebral pathology frequently complain of a memory loss. Some patients with epileptic seizures arising from the temporal lobe report a "memory" aura and "memory" responses are obtained occasionally from electrical stimulation of the temporal lobe. The aim of this project is to define the mechanisms of memory as they relate to normal and disturbed cerebral functioning. This project is closely related to the project Mechanisms of Memory, Branch of Surgical Neurology.

Proposed Course of the Project: As well as continuing the present line of investigation, the part played by personalized memory will be more carefully studied with the hope of determining a method of quantifying personal reminisence.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 69 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHERS	TOTAL
FY'57	$3,250	5,152	$8,402	.20	.33	.53

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	.33	.53	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 69 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB (70C)**
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Psychology
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Personality Characteristics of Temporal Lobe Epileptics.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin, Mildred Blevins, Robert Savard, Joyce Olhoeft
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To investigate the personalities of patients with epileptogenic lesions in one or the other or both temporal lobes to learn the function of the temporal lobe in personality.

Methods Employed: (a) Psychological tests of intelligence, personality, learning abstraction and speech which are administered to patients with epilepsy, primarily those with focal seizures who are candidates for surgical therapy. (b) Observation of patients. (c) Interviews.

Patient Material: (N-1-300)

		No.	Average Stay - days
Inpatient:	Adult Male	42	
	Adult Female	37	
	Child Male	6	
	Child Female	6	

Outpatient: Number of patients 34
Number of visits 34

Major Findings: Psychological testing indicates that a person with an epileptogenic focus in the dominant hemisphere tends to be relatively less adept in verbal skills; if the lesion is in the non-dominant hemisphere, the patient is relatively less adept in performance abilities.

Observation and interview techniques indicate that patients with an epileptogenic focus in the temporal lobe of the dominant hemisphere are poor communicators, they do not relate well to their family or to other people, they are relatively inactive physically, they use relatively few words in conversation, they do not elaborate their verbal responses, they do not appear to have a clear concept of themselves. Various combinations of these failings are noted in persons with epileptogenic lesions in other areas of the dominant hemisphere. From these data it may be possible through communication with the patient to lateralize if not localize intracerebral pathology and to begin to hazard some specific hypotheses regarding brain function, communication and personality.

Significance to the Program of the Institute: Personality defects are commonly reported in patients with seizures with an origin in the temporal lobe. This project hopes to define these personality defects and communication problems in order to assist the neurologists and neurosurgeons in the evaluation of seizure patients.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 70 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHERS	TOTAL
FY'57	$3,250	5,152	$8,402	.20	.33	.53

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	.33	.53	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 70 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 71 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Psychology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Speech Areas in Man
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Joyce Olhoeft, Maitland Baldwin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To localize brain areas involved in the production and interpretation of speech. To quantify and qualify the speech of persons with intracerebral pathology

Methods Employed: Testing the receptive and expressive speech of patients with intracerebral pathology using tests for aphasia and tests devised for the evaluation of speech errors other than aphasic errors. Speech testing of conscious patients while the exposed brain is being electrically stimulated. Pure tone audiometric examinations.

Patient Material: (N-1-302)

		No.	Average Stay - days
Inpatient:	Adult Male	14	
	Adult Female	23	
	Child Male	6	
	Child Female	11	
Outpatient:	Number of patients	12	
	Number of visits	20	

Major Findings: Patients with epileptogenic lesions in the dominant hemisphere are superior in speech tests using visual (pictures) stimuli than in those using auditory or written stimuli. The converse holds for patients with an epileptogenic lesion in the non-dominant hemisphere. Verbal abstraction abilities rank higher in patients with epileptogenic foci in the non-dominant hemisphere.

Significance to the Program of the Institute: Important speech centers lie in the posterior portions of the temporal lobe of the dominant hemisphere. There are indications that speech is modified in lesions of the non-dominant hemisphere. An analysis of the speech of persons with intracerebral pathology may lead to a further delineation of brain function as it is evaluated through speech. This project is related to the project: An Investigation of Speech Function Localized in the Temporal Areas of Man, Branch of Surgical Neurology.

Proposed Course of Project: Increased emphasis on audiometry and sound distortion and more precise methods of evaluating and comparing speech samples.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. **NINDB 71 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHERS	TOTAL
FY'57	$3,250	5,152	$8,402	.20	.33	.53

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	.33	.53	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 71 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 72 (C)**
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Psychology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The Role of the Temporal Lobe in Perception
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Mildred Blevins, Joyce Olhoeft, Maitland Baldwin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To determine the role of the temporal lobe in the perception of auditory, visual and tactile stimuli. Disorders of perception concurrent with chronic or acute intracerebral pathology.

Methods Employed: Tests of visual, auditory and tactual perception are administered to patients with intracerebral pathology.

Patient Material: (N-1-303)

		No.	Average Stay - days
Inpatient:	Adult Male	28	
	Adult Female	20	
	Child Male	0	
	Child Female	0	
Outpatient:	Number of patients	14	
	Number of visits	14	

Major Findings: Tests employing primarily visual stimuli indicate that once a visual perception has been interpreted by a person with intracerebral pathology it is difficult to force the person to change his interpretation with alterations in the visual stimulus. Tests comparing auditory and visual perception hint that auditory perception may be more changed than visual in patients with damage in the area of the temporal lobe of the dominant hemisphere. Tests of tactual perception show that spatial learning takes place through this modality in patients with epileptogenic foci in the temporal lobe. What seems to be lost to these patients is the ability to draw a picture of the tactual stimuli. This may indicate that tactual learning in these patients is not readily transferred to other modalities of learning.

Significance to the Program of the Institute: What is percieved, and how this perception is interpreted by an individual is a major part of personality. Some of these findings show alterations in perception and its interpretation in patients with brain pathology, particularly of the temporal lobe. Definition of these perceptual changes is important in understanding the functions of the temporal lobe.

Proposed Course of Project: Continuation in basically the same lines with increased emphasis on auditory perception and the apparent differences between auditory and visual perception.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. **NINDB 72 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57	$3,250	$5,152	$8,402	.20	.33	.53

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	.33	.53	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S):

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 72 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 73 (C)**
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Psychology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Intellectual and Social Evaluation of Severely Mentally Retarded Cerebral Palsied Individuals
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Anatole Dekaban, Joyce Olhoeft
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To attempt to measure more accurately the intellectual capacity and social adjustment potential of mentally retarded and severely physically handicapped cerebral palsied individuals.

Methods Employed: Standardized psychological tests that are at all practical are used. In nearly every case these are found to be inadequate due to the severe physical limitations of the patient. Attempts are made to establish conditioned reflexes utilizing such modalities of perception as are available to the individual. An evaluation of auditory acuity is attempted in each case.

Patient Material:

		No.	Average Stay - days
Inpatient:	Adult Male	1	
	Adult Female	1	
	Child Male	16	(N-9-801)
	Child Female	9	
Outpatient:	Number of patients	0	
	Number of visits	0	

Major Findings: The "developmental schedules" of Gesell and Cattell are helpful in appraising the motor, adaptive, language, and social developmental level of these handicapped patients, however, the results are frequently unrealistic when one compares the ages of the patients with the ages of the standardization group of these tests. The reliability of the results obtained with these tests is high, but the validity is probably low in many cases. Defects in vision and/or hearing preclude normal social responsiveness, hence, protracted observation of the patient is a necessary adjunct to evaluation. Five factors, obtained by observation, appear to be most helpful: (1) how long does it take the patient to "adjust" to the new surroundings? (2) how much interest does the patient show in his surroundings? (3) how much can the patient be taught? (4) does the patient appear to differentiate between the people around him (does he like some and not others)? (5) what attempts and through what modalities does he attempt to communicate? This latter factor may be the most important point: the patients who attempted to communicate, regardless of the severity of the physical defects, were always judged to be the most adequate; those whose attempts to communicate were meager or lacking altogether were most often judged the most severely handicapped regardless of the amount of physical difficulty.

The behaviour of some of these patients has seemed "autistic." This has been seen in those who are most intact physically and most non-communicative. This observation suggests a possible relationship between "autism" and "brain damage."

Significance to the Program of the Institute: To attempt to provide methods of evaluating the current status and future potential of severely handicapped children. Studies of brain function as measured by speech, motor skills, social relationships, and adaptibility are a major goal of this project, and as such are closely allied to the research of this institute as a whole.

Proposed Course of Project: To see if a relationship exists between the psychological findings and the physical findings, and to continue to refine the methods used to evaluate the patients.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 73 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHERS	TOTAL
FY'57	$2,500	5,152	7,652	.10	.35	.45

BUDGETED POSITIONS		
PROF	OTHER	TOTAL
FY'57 .10	.35	.45

PATIENT DAYS

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 73 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 74 (C)**
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Surgical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Psychology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Intellectual Status with Drug Change in the Cerebral Palsied Child.
PROJECT TITLE

7. Laurence L. Frost
PRINCIPAL INVESTIGATOR

8. Mildred Blevins, J. Gordan Millichap
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

10. PROJECT DESCRIPTION:

Objectives: To determine changes in intelligence of cerebral palsied children as measured by standardized psychological tests with changes in anti-convulsant medication.

Methods Employed: Standardized intelligence tests of the appropriate chronological age level are administered to children with cerebral palsy following changing and reestablishing them on various anti-convulsant medications, principally Diamox.

Patient Material: **(N-9-801)**

		No.	Average Stay - days
Inpatient:	Adult Male	0	
	Adult Female	0	
	Child Male	0	
	Child Female	0	

[redacted] Outpatient: Number of patients 6
Number of visits 6

Major Findings: No significant difference was found in the intelligence scores obtained by these patients following their establishment on Diamox. This indicated that regardless of the patients physical response to the change of medication or their response to Diamox, the intelligence test scores did not significantly change.

Significance to the Program of the Institute: This project indicated that Diamox did not significantly alter the patient's intelligence test scores.

Proposed Course of Project: This project is terminated.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. **NINDB 74 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHERS	TOTAL
FY'57	$2,500	5,152	$7,652	.10	.33	.43

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.10	.33	.43	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO. (S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. **NINDB 74 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 75 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness 3. Branch of Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service - Pain 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Respiratory Patterns
PROJECT TITLE

7. Kenneth D. Hall, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: The objective of this project is to study the respiratory patterns in patients and animals while awake and in different planes of anesthesia. It is also hoped to study the basic physiological respiratory responses of the patient by recording respiratory patterns during spontaneously breathing, controlled manual breathing and breathing with mechanical respirators, with and without muscle relaxants.

Method Employed: A wire screen flow meter was developed and built by this Section to record rapidly, accurately, and with as little resistance to the flow of respiratory gases as possible. With this, it is possible to record photographically the respiratory patterns simultaneously with other physiological parameters, such as arterial and venous blood pressures. From the record respiratory pattern can be measured or calculated: the respiratory rate, maximum instantaneous flow, tital air, and minute volume.

PROJECT DESCRIPTION (Continued)

Patient Material: None as yet **(N-6-524)**

Major Findings: None as yet

Significance to Neurological Research: It is hoped that it will be learned which methods of respiration are the most physiological and also that some light will be shed on the basic neurological problem of the control of respiration.

Proposed course of Project: At present the work on this project will be limited to recording normal asleep respirations, spontaneous and controlled on patients undergoing neurosurgical procedures under general anesthesia.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 75 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,500	5,152	$ 11,652	.33	.33	.66

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.33	.66	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 75 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH
INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. **NINDB 76 (C)**
SERIAL NUMBER

2. Neurological Diseases & Blindness 3. Branch of Surgical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service - **Pain** 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. Central Control of Autonomic Functions
PROJECT TITLE

7. Kenneth D. Hall, M. D.
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: The broad objective of this project will be to learn more of the central control of the various autonomic functions, such as blood pressure, respiration, etc.

Method Employed: At present one aspect of this project will be studied, namely, the phenomonen, known as the "Traube-Herring" waves. This will be done under light anesthesia with animals, recording: respiration, arterial and venous blood pressure, EKG's, and perhaps EEG's. It will be attempted to learn what level of anesthesia, if any, will obliterate these responses and also to study the effect on these waves of other physiological stimuli, such as hemorrhage. Eventually we hope to be able to study the effect of direct cortical stimulation on this phenomonen.

Patient Material: None as yet **(N-6-525)**

Major Findings: None as yet

PROJECT DESCRIPTION (Continued)

Significance to Neurological Research: It is hoped that this work may further explain some of the mechanisms of the control of the organism by the central nervous system.

Proposed course of Project: It is hoped that this project may be continued for sometime and will be studied in various parts. At present, Part I - Arterial Blood Pressure will be investigated.

PUBLIC HEALTHSERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 76 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$6,500	5,152 B	11,652	.33	.33	.66

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.33	.66	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 76 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A: Project Description Sheet 1. NINDB 77 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness 3. _____
INSTITUTE OR DIVISION LABORATORY, BRANCH OR DEPARTMENT

4. Neurosurgical Service - Pain 5. _____
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA

6. The Analgesic State
PROJECT TITLE

7. KENNETH D. HALL, M. D.
PRINCIPAL INVESTIGATOR

8. Forbes Norris, Jr., M. D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objective: There has been an increased interest in recent years in the so-called "analgesic state". The clinical use of this state has increased markedly and involves a large percentage of anesthesia in such fields as obstetrics, with its "twilight sleep" and "fearless childbirth"; plastic surgery, particularly during burn dressings, and grafts on poor risk patients; military surgery for emergency treatment of battle casualties, and cardiac surgery. Many drugs have been used in this connection, notably trichloroethylene, chloroform, and ether.

Although this state has been used widely clinically, very little studies have been done on the basic physiology involved. The techniques to measure the degree of the analgesic state and to separate it from the normal conscious state at one end and the anesthetic state at the other end have not been well worked out yet.

Method Employed: As an introduction to this project, we intend to investigate new drugs, for example, Fluothane, and study their effects on basic physiology and their analgesic and anesthetic properties first on experimental animals, and then, if deemed

PROJECT DESCRIPTION (Continued)

safe, on patients.

Patient Material: None as yet **(N-6-526)**

Major Findings: None as yet

Significance to Neurological Research: It is hoped that EEG and other techniques that measure responsiveness may enable us to reproducably achieve a state in which the patient or animal is conscious but feels no pain (with or without amnesia).

Proposed course of Project: Different aspects of this problem will be explored as they arise.

It is hoped that this work may also shed more light on the basic physiology of the nervous system.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 77 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,000	5,152	$18,152	1.33	.33	1.66

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1.33	.33	1.66	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE- - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 77 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

SUMMARY OF THE ACTIVITY
OF THE
BRANCH OF ELECTROENCEPHALOGRAPHY

The activity of the Branch has substantially increased during 1956.

EEG examinations for routine diagnosis and for research show a considerable increase over those performed in the previous years.

For 1956, at the date this report is being written (November 21st) a total of 1471 examinations were carried out on patients referred to the Branch from our Institute and other Institutes as follows:

	In Pts.	Out Pts.
NCI	307	15
NHI	34	10
NIAMD	36	2
NMI	40	1
NIMH	31	
NINDB	746	249
Totals	1194	277

Electrocorticographic studies during surgical exposure of the cerebral cortex were performed on 27 epileptic patients: and on 5 patients extensive study was carried out with chronically implanted electrodes. These figures of less than eleven months show an overall increase of 180 examinations over the previous calendar year.

A certain number of the above-mentioned examinations were performed as a part of the routine diagnostic service for various Institutes of the Clinical Center. The largest number of patients, however, were studied because they would fit into one or several research projects to be outlined in detail.

The major research project in the clinical field remains as in the two previous years, the study of the physiopathology of the epilepsies with particular emphasis on the group of focal lesions within the temporal lobe. This is a long-range project which needs the collection of a very large number of patients together with a careful and long follow-up study of operated subjects before drawing any definite conclusions.

Corollary of the first project, are projects **79** , **80** and **81** (electrocorticography, functional morphology and diagnostic significance of the epileptic seizure and study with chronically implanted electrodes). Project **80** has been terminated successfully and the very interesting data obtained have been collected and discussed in a monograph which has been recently accepted for publication in the form of a book. The results of project **79** will be presented and discussed in a colloquium to be held by the NINDB next March, as a preparation for a similar symposium at the International meeting for the League against Epilepsy in Brussels, next July.

The fourth project related to the project of epilepsy concerns a study with chronically implanted electrodes. Progress in this project is forcibly limited by risks involved in the technique and by the relatively small number of cases suitable for this type of study.

The project concerning the study of old age changes in the brain, and in particular the relationship between the cerebral blood flow and the electroencephalographic changes was continued throughout this year. This project has been started in collaboration with the NIMH and the Institute of Living of Hartford, Connecticut last year.

The EEG and neurological changes associated with the administration of a new drug (6-Azauracil) which seems to possess therapeutic effects upon leukemia, are the object of another project of research. The effects of this drug upon the electrical activity of the brain are quite striking. The lack of correlation between EEG pattern (markedly abnormal) and clinical signs (relatively insignificant) remains for the moment a puzzling problem. Further investigation is contemplated in the coming year on the same subject.

The 84 project is a research carried out in collaboration with the Section on Animal Behavior of the Laboratory of Psychology of the NIMH. It concerns the study of continuous performance test in epileptics correlating the performance itself with the amount of electrographic abnormalities in various diagnostic groups of epileptics.

In the field of experimental epilepsy, a project was recently completed and the elaboration of the findings and their publication should take place in the near future. This project deals with the study of electrographic behavior and distribution of paroxysmal discharges similar to those commonly observed in cases of human epilepsy but artificially reproduced in various cortical regions and various subcortical structures of cats and monkeys.

The subcortical control of certain cortical rhythms has been the object of another experimental study (Project 86). It deals particularly with the mechanism of spindles which characterize the electrical activity of the brain in certain experimental conditions, and it has indirect bearings on the problem of centrencephalic epilepsy and related disorders. This project has been completed and the manuscript accepted for publication, and the final paper should come out at the end of the year.

The section of Clinical Neurophysiology has been without a chief investigator for a certain time, and the position is at present still vacant. The activity of that section, therefore, has been forcibly reduced, and only one project of research (Effect of temperature on the neuromuscular junction) was carried out by this Section during the last year.

During the past year the staff of the Branch of Electroencephalography has been increased and includes at the present time 3 EEG technicians, 1 trainee technician, and 1 technician in experimental neurology. In addition, three research associates have joined our Branch during the last year, alternating in collaborating very actively on several of the research projects.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 78 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Electroencephalography
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Temporal lobe epilepsy, electrographic study.
PROJECT TITLE

7. Cosimo Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. Maitland Baldwin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION **(N-1-601)**

Objectives: The main objective of this project is to establish reliable criteria to arrive at a correct electroencephalographic diagnosis of this form of epilepsy, and to obtain further information on its physiopathogenetic mechanisms.

Methods employed and patient material: This main project is subdivided into the following sub-sections:

a) EEG study of the interseizure period
b) EEG study of the ictal episodes
c) Effects of sleep "activation"
d) EEG-pathological correlations
e) Electrographic manifestations of subcortical epileptogenic lesions.

Routine EEG examinations are performed on all epileptic patients admitted by the Neurosurgical Branch (and by the Neurology Branch for comparison). From a minimum of 3 up to over 15 tracings are obtained on each patient in various conditions (while the patient is on medication, after withdrawal of medication, during induced sleep, during spontaneous and/or induced seizures, etc.) using a minimum of 21 electrodes, including particular placements like pharyngeal electrodes and various methods of localization. Grass EEG machines at 8 and (more recently) 16 channels are used. In patients who eventually undergo surgical treatment, a systematic post-operative follow-up is carried out.

Major findings: Useful and reliable results in this long range project can only be obtained after having studied a large number of cases in which a definite clinical-pathological diagnosis was eventually established through operation. To assess the results of surgical treatment in these cases one has to wait for a minimum of one up to five years of post-operative follow-up. To date the number of these follow-ups, long enough to be considered useful and reliable, is too little to allow any definite conclusions. Various points of practical interest are worth mentioning, however, keeping in mind the above-mentioned limitations. 1) There exists a surprisingly high number of temporal lobe cases with evidence of bilateral involvement. 2) A diagnosis based solely upon the study of the interseizure period is generally unreliable: a case which would be considered clearly unilateral on the basis of this study might show a contralateral activation during an attack or a bitemporal activation during another attack. 3) Although the large majority of cases tends to show electrographic evidence of an epileptogenic focus in the anterior portion of the temporal lobe, there is a certain percentage of patients who show, instead, a focus in the middle or posterior portion of the temporal lobe. This different localization appears to be correlated with different clinical seizure patterns; however, it is not yet established with certainty which particular structure or portion within the temporal lobe itself is involved in either case, and whether one or the other type of epileptogenic lesion is more susceptible to surgical treatment. 4) The puzzling problem of possible involvement of subcortical structures, either deep within the temporal lobe or even deeper somewhere in the brain stem remains unsolved. Some of the electrographic criteria suggesting a subcortical involvement were outlined, but lack of convincing evidence to prove or disprove the electrographic diagnosis prevents one from drawing definite conclusions. Other findings of a certain interest related to the general problem are reported under separate projects related to focal epilepsy in general and, indirectly, also to temporal lobe seizures.

Significance to the program of the Institute: The most important program of the Neurosurgical Branch of the NINDB concerns temporal lobe epilepsy, and, therefore, this particular research project of the Branch of Electroencephalography is of primary importance and the necessary correlate for one of the main projects carried on by the Institute.

Proposed course of project: Fundamentally unchanged. The recent purchase of a 16 channel EEG machine, the increased number of cases and the progressively increasing follow-ups are expected to yield more concrete results and allow more definite conclusions on this subject of research.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 78 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$12,400	5,151	$17,551	.25	2.	2.25

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.25	2.	2.25	

13. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

BIOLOGIC STANDARDS [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 78 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 79 (C)**
SERIAL NUMBER

2. **Neurological Diseases & Blindness**
INSTITUTE OR DIVISION

3. **Electroencephalography**
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Electrocorticography in focal epilepsy.
PROJECT TITLE

7. Cosimo Ajmone Marsan
PRINCIPAL INVESTIGATORS

8. Maitland Baldwin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The two main objectives of this project are: a) to study the topography and the behavior of the abnormal discharges directly from the exposed human cortex in cases of focal cerebral seizures originating in different regions. For practical purposes temporal lobe cases are studied separately from the non-temporal cases. b) a direct study of the electrical activity of different cortical regions of the human brain under various conditions (normal, sleep, drugs, hypothermia, electrical stimulation, etc.).

Methods employed and patient material: This study is performed on all the epileptic patients selected for surgical treatment. A certain number of other non-epileptic patients was also used. **(N-1-601)**

Electrical recording is carried out by means of ten cortical electrodes and an 8 channel EEG apparatus.

Major findings: The evaluation of the data obtained is carried out in two steps. In the first step an extemporaneous interpretation is attempted at the very moment of the recording in order to provide the neurosurgeon with the information necessary to outline the areas of the cortex which are considered responsible for the epileptic attacks, and to carry on their ablation. The second step consists of a careful and detailed study of the records at a later date, comparing the findings, not only with the pre-operative electroencephalograms but also with the post-operative tracings, and to correlate them with the result of operation. The data of some 90 cases obtained with the above-described method are now in the process of being reviewed and correlated. Those concerning electrocorticography in temporal lobe epilepsy will be presented and discussed on the occasion of a colloquium on Temporal Lobe Epilepsy in March, 1957 (Bethesda), and at the International meeting next July (Brussels). In regard to abnormal discharges of an epileptiform type, some interesting observations were made concerning their topographical distribution, form, organization, susceptibility to arousal stimuli, etc. The characteristics of electrically induced afterdischarges in both normal and abnormal tissue were studied. The effect of cortical undercutting upon the epileptic discharge was investigated, as well as the "activating" effect of cortical excision upon the remaining structures. The significance of positive or negative correlations between the EEG abnormalities and the abnormalities which can be recorded from the exposed cortex are still a matter of investigation, and definite conclusions for this as well as for other related problems cannot be drawn until a sufficiently large number of cases with a long enough follow-up study are available. The behavior of the "normal" spontaneous activity, and its modifications following different procedures or under the effect of different agents, is also under study.

Significance to the program of the Institute: This project is a primary adjunct to the research of the Neurosurgical Branch. It is directly related to the project on temporal lobe epilepsy.

Proposed course of project: More extensive and careful study of the parameters of electrical stimulation. Depth recording as well as cortical recording. Collection of a larger number of cases.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. **NINDB 79 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	H 11,000	5,151	H 16,151	.25	1.	1.25

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.25	1.	1.25	

13. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

BIOLOGIC STANDARDS [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C· Honors, Awards & Publications 15. **NINDB 79 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 80 (C)**
SERIAL NUMBER

2. **Neurological Diseases & Blindness**
INSTITUTE OR DIVISION

3. **Electroencephalography**
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. The epileptic seizure. Its functional morphology and diagnostic significance.
PROJECT TITLE

7. Cosimo Ajmone Marsan and Bruce L. Ralston
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: This is a clinical-electrographic analysis of Metrazol induced attacks. The main objectives are 1) to produce convincing evidence for assessing the validity and usefulness of Metrazol activation, 2) to establish criteria of localization and lateralization of an epileptogenic lesion, 3) to obtain more precise information on the electrographic correlates of the various clinical manifestations occurring during a seizure, 4) to provide reasonable interpretations on the mechanisms underlying the spread of epileptic activation originating from different cortical areas.

Methods employed and patient material: The Metrazol is administered by slow intravenous injection according to the method of Jasper and Courtois 1952. Over 150 seizures were induced in 119 epileptic patients. The Clinical changes occurring in the pre-ictal, ictal, and post-ictal periods are carefully recorded by means of photography (serial single frames at

different intervals throughout the procedure) and by the use of a dictating machine (continuous dictating of the description of objective and subjective signs occurring throughout the injection of Metrazol and the development of the seizure). Patients were selected from among the epileptic population, mostly admitted by the Neurosurgical Branch and in which surgical treatment was contemplated. (N-1-603)

Major findings: In the differential diagnosis and classification of the various forms of focal epilepsy, the importance of the aura and the very first signs at the beginning of an attack are unquestionable, and in the large majority of cases this clinical criteria are considered the only ones of practical value for localization of the epileptogenic process. Yet a specific aura is very seldom present or recognizable and, when present, does not always help in lateralizing the lesion. In the case of a spontaneous attack, the early signs, even when they would have a clearly localizing and lateralizing character, are very often missed for obvious reasons. In this study the pattern of the entire epileptic seizure could be studied in detail and emphasis is placed not only on the different signs at the beginning of the attack: all symptoms and their temporal relationships in the course of the attack were considered. Pre-ictal, ictal and post-ictal clinical symptoms are discussed and integrated with their electrographic correlates. Various "seizure formulae" can be composed on the basis of the various clinical EEG criteria established in the above-mentioned series of patients in which the correct diagnosis had been previously established in all cases, and subsequently confirmed at operation in the large majority. The value and reliability of the different lateralizing signs are discussed. Commonly unrecognized features in the course of various seizure patterns are described which proved to be of importance in the topographical diagnosis of the epileptogenic focus. Criteria for correctly interpreting EEGs which are apparently negative or become diffusely abnormal during the development of an attack, are suggested so that indirect localizing information can be obtained and the number of useful results significantly increased. All these and other data were collected in a recently completed monograph which includes a critical and detailed review of purposes, methods and results of the EEG activation by means of Metrazol administration, and which has been accepted for publication (C. C. Thomas).

Significance to the program of the Institute: This project is closely related to the project regarding temporal lobe epilepsy and the focal epilepsy in general, which are two of the main projects of our Branch and of the Neurosurgical Branch. It was originally incorporated in the first project mentioned.

Proposed course of project: This project is considered finished; however, data are still collected in the course of routine activating procedures carried out on epileptic patients. The recent addition of a 16 channel EEG machine will provide further useful information for the obvious reasons that the amount of information increases when there is the possibility of recording simultaneously from a larger number of brain areas during the induced attack. Also the improvement in the photographic recording (which is presently in the process of being worked out) will increase the amount of useful data in this study.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 80 C
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,000	5,151	$ 16,151	.25	1.	1.25

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.25	1.	1.25	

13. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ PROFESSIONAL & TECHNICAL ASSISTANCE ☐

BIOLOGIC STANDARDS ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 80 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

The Epileptic Seizure - Its functional morphology and diagnostic significance

(a clinical-electrographic analysis of Metrazol-induced attacks)

Accepted for publication by C. C. Thomas, Springfield, Illinois

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 81 (C)**
SERIAL NUMBER

2. **Neurological Diseases & Blindness**
INSTITUTE OR DIVISION

3. **Electroencephalography**
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Implanted electrodes in humans. Depth recording and stimulation in epileptic patients.
PROJECT TITLE

7. Cosimo Ajmone Marsan
PRINCIPAL INVESTIGATOR

8. John Van Buren and Choh luh Li
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The main purpose of this project is to study the electrical activity of deeply located structures and of the cerebral cortex with chronically implanted electrodes. This, in order to gain further diagnostic information on patients who are candidates for surgery.

Methods employed and patient material: The method of the implanted electrodes in humans is still in the experimental phase, and in view of the risks involved in the technique, these studies have been applied to date only on highly selected cases. The major criteria for the selection has been the severity of the epileptic syndrome, the almost final decision concerning surgical therapy, and the lack of definite information with the routine EEG procedure. Since this project was started during the middle of last year, only 5 patients were found suitable for this investigation. The electrodes for implantation have been designed

by Dr. Choh luh Li, and made in the Instrument Shop of the Institute. In brief, they consist of 7 contacts, 4 of which are meant to record or stimulate from deep structures and 3 from superficial structures either sub- or extradural. Different electrodes providing 7 contacts entirely superficial could also be used at times. These electrodes are implanted under sterile conditions through a burr hole overlying the area to be surveyed. Implantation was carried out either unilaterally or bilaterally; this last instance in cases of temporal lobe involvement. The electrodes are left in place from 5 to 7 days and eventually removed. **(N-1-606)**

Major findings: In view of the small number of cases studied up to now, only sporadic and scattered information can be reported. First it has been possible to study the electrical activity directly from the cortex of a completely unanesthetized patient under normal conditions, during sleep, during Metrazol activation, during and following electrical stimulation of different regions through the same electrodes. By simultaneous study it has been possible to compare these results with the information obtainable through the routine scalp EEG recording, under the same conditions. In some cases it has been possible to determine the side of maximal firing in patients in which the routine scalp EEG would only show bilateral involvement without any clear predominance of side. On the other hand, the reverse was also true, and in cases which would show maximal involvement with the routine scalp EEG turn out to be definitely bilateral as a result of depth electrode study. One of the most common findings was the marked asynchronicity of the paroxysmal discharges indicating probably the existance of multiple foci or of a focus located deeper and firing asynchronously to different regions.

The main weakness of the method employed consists of the impossibility of accurately locating the tip of the recording depth electrodes: therefore, in the field of localization one has the impression that with this method he is merely shifting the problem but not solving it. Interesting observations were made on the behavior and spread or projection of the epileptiform discharges. It seems that the amplitude *per se* is not the only factor responsible for a spike to be recorded at the cortical level when originating in deeper structures.

Significance to the program of the Institute: This project integrates with the other projects related to the study of focal epilepsy, and, in particular, temporal lobe epilepsy, and is a very useful correlate study to those projects.

Proposed course of project: Fundamentally unchanged. Attempts will be made to better localize the recording and stimulating electrodes. The main difficulty remains the selection of patients suitable for this particular research project in view of the theoretical risks involved in the procedure itself.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. **NINDB 81 (C)**
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$11,000	5,151	$ 16,151	.25	1.	1.25

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.25	1.	1.25	

13. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW & APPROVAL ☐ PROFESSIONAL & TECHNICAL ASSISTANCE ☐

BIOLOGIC STANDARDS ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 81 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 82 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Electroencephalography
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. Hartford, Connecticut
LOCATION (IF OTHER THAN BETHESDA)

6. Electroencephalographic study and cerebral blood flow in old age.
PROJECT TITLE

7. Walter D. Obrist
PRINCIPAL INVESTIGATOR

8. Cosimo Ajmone Marsan, J. Birran and others
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: To study the correlations between the EEG pattern of old individuals (normal subjects) and their cerebral blood flow.

Methods employed and patient material: Subjects are provided by the NIMH. A routine EEG examination is carried out, and in addition, tape recording for use in electronic frequency analysis. All tape recordings are obtained from bipolar runs involving three areas: fronto-central, middle posterior temporal and parietal-occipital.

Major findings: Still to be processed.

Significance to the program of the Institute: This project is primarily one of the NIMH, and the part performed by this Branch integrates one of their main projects, which consists of a general study of old age.

Proposed course of project: About 50 subjects are to be investigated, and therefore, the project will be carried out during the coming year without significant modifications in methodology.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 82 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	X	ADMINISTRATION	
REVIEW & APPROVAL		PROFESSIONAL & TECHNICAL ASSISTANCE	
BIOLOGIC STANDARDS			

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 82 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

ORP-1 Callendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 83 (C)**
SERIAL NUMBER

2. **Neurological Diseases & Blindness**
INSTITUTE OR DIVISION

3. **Electroencephalography**
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Electroencephalographic and neurological changes associated with 6-Aza-uracil administration.
PROJECT TITLE

7. Charles E. Wells and Cosimo Ajmone Marsan
PRINCIPAL INVESTIGATORS

8. Emil Frei
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The purpose of this project is to determine the central nervous system effect of a new drug which is being used to treat leukemic and cancer patients.

Methods employed and patient material: This study is carried out on patients referred to this Branch, mostly by the NCI (leukemia and cancer Sections). To date, 20 patients have been examined by this Branch from both a neurological and EEG standpoint. Serial EEG examinations are performed on each patient from a minimum of 5 up to 20 or more. Routine records are taken, together with hyperventilation, sleep and various physiological stimulations.

Major findings: The most dramatic changes elicited by 6-Azauracil on the CNS are definitely those observable through the study of the electrical activity of the brain. Within a variable interval of time following the beginning of "treatment", the EEG undergoes marked changes with appearance of very slow rhythms, diffuse, bilateral and fairly rhythmical. These changes appear easier to be elicited in children, however, adults too, show a large amount of abnormalities. The normal rhythms disappear completely and in particular, the fast activity is completely abolished. The patients who show a good driving response to photic stimulation prior to the administration of the drug fail to show this response after the "treatment" has started. The EEG changes seem to precede the clinical changes, and, as a matter of fact, one of the striking features in this study is the discrepancy between electrographic and clinical changes: the EEG record can be at times indistinguishable from those obtained in comatose patients, and yet, in the case of 6-Azauracil, the patient is alert or only slightly drowsy. The effect of the drug is reversible, and the record returns to normal within a few days following the interruption of the treatment. Unfortunately, the above-described changes in the EEG do not seem to be reproducible in animals. No appreciable changes could, in fact,be elicited in 2 cats following intravenous administration of an exceedingly high dose of 6-Azauracil (about 1000 mgs/Kg). For this reason it is difficult to study experimentally the mechanisms underlying the above-described electrographic changes, and therefore, it is not possible at this time to determine whether this drug acts primarily upon the cortex or upon subcortical centers, or on both in a diffuse way.

Significance to the program of the Institute: This project is primarily a correlate of a project of the NCI. The involvement (direct or indirect?) of the arousal system, following administration of this drug, is obvious, and, therefore, the project itself fits into other projects of the Institute related to the mechanisms underlying alteration of awareness, attention and consciousness.

Proposed course of project: A preliminary report on the effect of the drug will be presented at the next meeting of the Eastern EEG Association. The investigation is, however, carried out, and it is planned to try experimentally the effect of the drug on young animals, to see whether they are more susceptible as in the case of humans, with the aim of gaining more knowledge in the mechanisms underlying the effect of the drug.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. **NINDB 83 (C)**
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$6,000	5,151	$11,151	.5	0	.5

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.5	0	.5	

13. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

BIOLOGIC STANDARDS [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

NCI C4-709 - Leukemia
NCI C5-712 - Cancer

(Use reverse and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 83 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

ORP-1 Callendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 84 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Electroencephalography
LABORATORY, BRANCH, OR DEPARTMENT

4.
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Continuous performance test in epileptics.
PROJECT TITLE

7. Allen F. Mirsky
PRINCIPAL INVESTIGATOR

8. Cosimo Ajmone Marsan
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The purpose of this project is to determine the presence and degree of impairment "for the continuous performance test" in epileptic patients.

Methods employed and patient material: The main part of this project is carried out by the Section on Animal Behavior of the Laboratory of Psychology of the NIMH. The activity of the Branch of EEG in this project consists mainly in selecting the patients to be tested according to localization and degree of abnormalities. Further details are to be found in the project description of the NIMH report.

Major findings: See NIMH report.

Significance to the program of the Institute: The determination of the validity of this test and of the reliability of selective impairment in different groups of focal cerebral seizures is very important. An additional tool would thus be added in the diagnosis of focal epilepsy which is one of the main problems of the Institute.

Proposed course of project: See NIMH report.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 84 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW & APPROVAL [ ] PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

BIOLOGIC STANDARDS [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 84 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

ORP-1 Callendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 85 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Electroencephalography
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Experimental epilepsy. Electrographic studies in experimentally produced epileptogenic lesions in cortical and subcortical structures.
PROJECT TITLE

7. Bruce L. Ralston
PRINCIPAL INVESTIGATOR

8. Cosimo Ajmone Marsan
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The purpose of this project which was started during the previous year, is to study the electrographic behavior and distribution of paroxysmal discharges similar to those commonly observed in cases of human epilepsy but artificially produced (strychnine or penicillin) in various cortical regions and various subcortical structures.

Methods employed and patient material: Acute experiments were performed on cats and monkeys with or without general anesthesia. Epileptogenic lesions were produced with Penicillin or Strychnine and the drugs were introduced by means of stereotaxically oriented needles. Cortical and subcortical recordings by means of an 8 channel Offner EEG apparatus and a Dumont CRO.

Major findings: The results obtained in over 50 animals are still in the process of being elaborated. Interesting observations were made on the general pattern of the induced epileptiform activity which seems to have particular features depending on the various localizations within the cortex and subcortical structures. Of particular interest was the study of the transition between the stage of sporadic spikes and the state of electrographic seizure. It was found that even though the epileptiform abnormalities tend to become diffuse and spread over wide areas of both hemispheres following the production of a discrete lesion, the development of a "seizure" activity either spontaneous or induced (Metrazol) tends, at least at the beginning, to remain fairly well localized and possesses characteristic features allowing the localization of the original focus even in the presence of widely diffuse abnormalities. The particular behavior of lesions located along the midline (supplementary motor and cingulate regions in particular) have been studied.

Significance to the program of the Institute: The possibility of establishing criteria for selecting cases of cortical from those with subcortical lesions, is of practical significance. As the main clinical project of this Branch and of the Institute is the study of focal epilepsy, the significance of the data experimentally obtained becomes evident.

Proposed course of project: This project is considered complete. Elaboration of the findings and their publication should take place in the very near future.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 85 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,000	5,151	$ 8,151	.25		.25

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.25		.25	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 85 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. **NINDB 86 (C)**
SERIAL NUMBER

2. **Neurological Diseases & Blindness**
INSTITUTE OR DIVISION

3. **Electroencephalography**
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Thalamic control of certain normal and abnormal cortical rhythms.
PROJECT TITLE

7. Bruce L. Ralston
PRINCIPAL INVESTIGATOR

8. Cosimo Ajmone Marsan
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The mechanism of production of certain types of electrical activity of the brain is still a controversial matter. The origin of many characteristic electrographic patterns which can be observed under different experimental conditions as well as the origin of many physiological or pathological rhythms which can be recorded in the human EEG are still obscure. The problem of determining the origin of various spontaneous rhythms is of obvious theoretical interest, and the correct interpretation of a given pathological potential becomes, on the other hand, a matter of practical importance in the field of clinical EEG. The purpose of this project is to determine some of the factors involved in the mechanism of production of barbiturate spindles by analyzing the modifications which these undergo following subcortical lesions of a certain type and location. These lesions were made with Penicillin,

an agent possessing well known epileptogenic qualities. As this agent, when injected into the thalamus, proved capable of producing a picture of sporadic paroxysmal high voltage bursts of slow and sharp waves either unilaterally or bilaterally synchronous, the question of relationship to certain pathological human rhythms and to the so-called centrencephalic epilepsy can also be raised in the discussion of the findings.

Methods employed and patient material: A total of 60 animals was studied; in these, Penicillin (aqueous Squibb) was injected by micrometric control into the various portions of the thalamus in amounts ranging from .0025cc to .015cc. Other animals had isotonic saline in similar amounts deposited on the same side to act as controls. All animals were anesthetized and placed in a stereotaxic apparatus. Anesthesia was maintained by intravenous Pentothal given in small increments just sufficient to produce active 8-12/sec spindle bursts. Occasionally, supplementary Curare and artificial respiration were employed. A few animals were initially anesthetized with ether and then maintained on Curare and artificial respiration in order to study the effects of the thalamic lesion on the waking electrocorticogram. Cortical recording was done through bipolar silver electrodes with a 2-3mm interelectrode distance. Penicillin was introduced with a #22 spinal needle mounted on a stereotaxic carried introduced horizontally from behind. This needle was insulated down to the tip and was left in place at the site of the injection as a recording electrode. Placement of Penicillin was determined by preliminary stimulation, utilizing the recruiting response for the aspecific thalamic system and a short latency revoked response of specific projection nuclei for guidance. The Penicillin in controlled saline injections was colored with Cresyl violet to check on diffusion from the injected side. All placements were verified by frozen sections 50 microns thick and stained by the Nissel and Weil techniques. Recording was carried out with an 8 channel Offner EEG apparatus with provision made for monitoring 2 channels at a time with a DuMont CRO. Continuous recording at different speeds was made for a minimum of 5 hours and usually from 7 to 10 hours.

Major findings: 1. Injection of small amounts of Penicillin in various areas of the thalamus of cats under barbiturate anesthesia is routinely followed by slowing of the 8-12/sec barbiturate spindle to 3.5-5/sec, and by spindle synchronization. Such an end result also occurs in the unanesthetized preparation, although it may be accentuated by barbiturates. 2. The distribution of the spindle alteration depends upon the location of the thalamic imjection. 3. Evidence is given to suggest that these changes are mediated through the nonspecific thalamic system, and that they are not necessarily dependent upon elimination of arousal mechanisms. 4. These results would confirm the hypothesis that the thalamus is very likely the anatomo-physiological substrate for the rhythmical 8-12/sec barbiturate spindle and that in regard to this particular type of electrical activity, the cerebral cortex is only secondarily activated by impulses of subcortical origin.

Significance to the program of the Institute: It is possible that the discharges of the so-called centrencephalic epilepsy as well as those of other forms of subcortical epilepsy, are the result of lesions "firing" via a similar mechanism.

Proposed course of project: This project is considered finished. A manuscript was prepared, has been accepted for publication and is expected to appear within 1956 in the Journal of EEG and Clinical Neurophysiology.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 86 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,000	5,151	$8,151	.25		.25

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.25		.25	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. **NINDB 86 (C)**
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Thalamic control of certain normal and abnormal cortical rhythms.

EEG and Clin. Neurophysiol. November issue 1956 (in press).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

ORP-1 Callendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 87 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Electroencephalography
LABORATORY, BRANCH, OR DEPARTMENT

4. _____
SECTION OR SERVICE

5. _____
LOCATION (IF OTHER THAN BETHESDA)

6. Effect of temperature on the mammalian neuromuscular function.
PROJECT TITLE

7. Paul O. Chatfield and Alexander Doudoumopolous
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

Objectives: The purpose of this project is to study in detail the effects of variation of temperature and particularly of cold upon the neuromuscular preparation in rat.

Methods employed and patient material: The experiments are carried out on rats anesthetized with barbiturate. One sciatic nerve is exposed, placed upon stimulating electrodes and ligated after having been crushed proximally to the electrodes. The corresponding gastrocnemius muscle is freed from its insertion at the ankle and its tendon is attached to a strain gauge for isometric recording of muscular contractions. The potential changes from the strain gauge are led into a DC amplifier and then recorded photographically with a cathode ray oscilloscope. A thermocouple is inserted in the muscle and the variations of the local tempera-

ture are recorded with a suitable apparatus. Electrical stimulation is carried out with a Grass stimulator. Parameters of stimulation are varied: single pulse and tetanizing current is used. The same procedure is used at 37°, 28°, 18° and 9° of temperature, and the results are compared and tabulated.

Major findings: Preliminary results would indicate that lowering of the temperature has no significant effect upon the transmission through the neuromuscular junctions.

Significance to the program of the Institute: This experimental project integrates with the broader program of the Institute related to the problem of neuromuscular diseases.

Proposed course of project: The project is expected to be terminated by the end of the year. The effect of temperature upon the action muscle potential will also be investigated and the results compared with the effect of temperature upon tension.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

11. NINDB 87 (C)
SERIAL NUMBER

Part B: Budget Data

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$21,500	5,151	$ 26,651	1	2	3

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1	2	3	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

(Use reverse and additional pages, if necessary)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 87 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

(Use reverse side and additional pages, if necessary)

Annual Report
Medical Neurology Branch
National Institute of Neurological
Diseases and Blindness October 1956

SUMMARY

Two-hundred patients were admitted to the Medical Neurology Branch over the current calendar year of November 1955 to November 1956. In addition to the ward unit all laboratories, with the exception of the Section of Neuroradiology, were activated during the current year. With the addition of further permanent staff to fill the laboratories in personnel, the fields of research will cover a broader spectrum than had hitherto been noted. Seven of the projects herein listed are projected toward the future calendar year and are the natural outgrowth of previous work of the past year. Twenty-five publications and three books are in preparation or have been published during the current year. One administrative change was made in the branch during the current year in that the Section on Clinical Neurophysiology has been shifted to the Electroencephalography Branch. The only loss in the permanent organization for the year within the Institute was in this section with the resignation of Dr. Paul O. Chatfield. This position being temporarily vacated, therefore, no future projects will be indicated until a new head of this section is appointed. Past projects within this section will be reported in the Branch of Electroencephalography. This, then, leaves but three sections to be reported by this Branch: The Section of Clinical Neurochemistry, the Section of Applied Pharmacology, and the Section of Applied Biophysics.

Much of the work in the Section of Clinical Neurochemistry has continued in the further elucidation of amino acid metabolism, electrolyte metabolism, and acetylcholine metabolism within the brain. With the entry by Dr. Tower (2½ years ago) into the administration of large quantities of glutamine and asparagine in seizure patients, it became necessary to find new techniques to assay these in blood and spinal fluid. The utilization of dinitrophenyl-amino-acid-column-chromatograph has led to more difficulties than had been anticipated. These difficulties have been encountered in units other than this institute so that analysis of glutamic acid and aspartic acid amides in vivo are now probably going to have to be done through the utilization of microelectrode techniques. The utilization of guinea pig asparaginase enzyme has, however, given some indication as to the metabolism of asparagine. Peak levels have been obtained similar to those found with the dinitrophenyl-column method. The serum values reach their height in approximately one hour and fall to normal in approximately three to four hours. Twenty-four-hour urinary excretion is not in excess of normal, showing that asparagine is metabolized. C-14 labeled asparagine has recently become available in a purified form, the purification of which

was worked out by Dr. Tower in his laboratory. Aspartic acid under these conditions has been metabolized more readily in tissue slices with C-14 activity noted in the following compounds: glutamic acid, glutamine, and gamma-amino-butyric acid. Asparagine under the same conditions was less readily utilized but again C-14 was found in aspartic acid, glutamic acid, glutamine, and gamma-amino-butyric acid. The isotopically labeled compounds were labeled on the second and fourth carbons of asparagine and aspartic acid. Since these two carbon atoms are not available for utilization in decarboxylation in the Krebbs cycle, they are not, therefore, lost to other metabolytes during this study. Over 50 patients have now been admitted to this Institute and 200 to allied institutes for the studying of the anticonvulsive effects of these amino acids. At the last meeting of the cooperative units the following conclusions were reached:

Percentage significantly improved by asparagine----------40
Percentage not benefited----------50
Percentage with increased seizure activity----------10
Percentage with EEG improvement----------25
Percentage with severe sight reactions----------15

As a result of this, plus experimental data obtained by the research division of Merck & Co. on gamma-amino-butyrate and its lactam 2-pyrrolidinone indicating anticonvulsant activity for these two compounds, a modification of this project has begun. Patients now on asparagine are being started on these two compounds in order to assess their clinical efficacy. This, again, has necessitated development of methods for their detection. It is anticipated that the dinitrophenyl derivitive of gamma-amino-butyrate can be found and isolated by column chromatography. 2-pyrrolidinone can be converted to the 2-thio derivatives in the presence of P_2S_5 and then spectrophotometrically worked out. Along with this, the pharmacological properties of 2-thio-pyrrolidinone have been worked out by Dr. Irwin and his unit. The addition of either of the two above compounds will also cause a revision to normal of epileptic slices of brain insofar as glutamine and glutamic acid. Each of these substances will also reverse seizures in cats which have been induced by methyl-ethyl-glutarimide (M.E.G.). So far, however, in epileptic mice Dr. Irwin has found that 2-pyrrolidinone is an analgesic without hypnosis but is not an effective anticonvulsant.

Dr. Horvath is continuing his studies in the proteins of muscle in diseases and normal states. He has found in his work on glycerinated fibers and on actomyosin threads, that there is a limited range of ATP concentrations where contraction occurs. There appears to be a difference between normal and myotonic muscle in the extent of this range. Ultracentrifuge studies indicate that myosin prepared from patients with Muscular Dystrophy is polydisperse. Normal muscle yields muscle that is monodisperse. Each fraction is characterized by a different sedimentation constant in the ultracentrifuge. Dr. Horvath's previous project on smooth

and striated muscle actomyosin comparisons has been delayed because of these new findings and their application, and it is projected again for the next year.

Dr. Wells and Dr. Haase have continued their studies on concentration of vitamin B_{12} levels from the cerebrospinal fluid to see if there is a concentration in the spinal fluid of this after large doses. Difficulties have been encountered in the extraction procedure and in the erratic growth of the test organism. The majority of samples, therefore, have not been assayed since their validity would be liable to question and will be kept frozen until experimental conditions are more standardized.

Further studies in the appearance of gamma globulin in demylinizing diseases (which have been shown to be increased in earlier studies) are being undertaken by Dr. Curtis by use of enzymatic kinetics with a suitable agent, L-asparaginase, from guinea pig serum. Dr. Curtis is also continuing the study of nature and characteristics of urinary polypeptides in neurological diseases which he has already isolated from patients with muscular dystrophy. He is particularly interested in the oxyproteic acid constituents.

The finding of as little as 0.1 mcg. of acetylcholine can be detected by fluorescence in the presence of tetra-phenyl-diboronoxide has given, for the first time, a method for accurate determination of acetylcholine. As this substance is essential in neuromuscular transmission, this new procedure promises much.

The description of a disease by Jepson in England, which occurred familially with cerebellar disturbances has aroused much interest in that a specific indole was found in this disorder. It is possible that other degenerative disorders may lie in an abnormality of phenylalanine-tyrosine metabolism and this will be investigated in the current year by Dr. King Engel and Dr. Tower. Similar studies will be carried on by Dr. Dekaban and Dr. Tower on patients with phenylketonuria.

The Section of Neuropharmacology has developed an expanding program with the return of Dr. Irwin to the unit. The agents studied by this unit are the depolarizing and competitive drugs acting upon neuro-transmission. The unit completed this year the highly technical procedure of determining central effects of certain of these depolarizing compounds by use of the isolated closed transfusion technique to the head of a recipient dog by a donor dog. The finding that in the dog the anterior spinal artery supplies respiratory centers of the brain stem led to the development of additional techniques for compressing this artery and the returning venous blood in spinal canal. When this was done, it was found that (unlike previous reports had indicated) these agents had no central action upon the respiratory system. Dr. Irwin, Mr. Wells and Dr. Rowley are continuing work on the effect of these drugs on innervated and denervated muscle. They find the

neuromuscular blocking agents which provide transmission by initial depolarization of the motor end plate reduces the contraction of directly stimulated muscle by an average of 50%. Those compounds, however, which are known to compete with acethylcholine for receptor sites (curare) do not influence contraction following direct stimulation of muscle. Indirect evidence indicates that the action of depolarizing compounds in innervated muscle does not arise from the spreading of depolarization from the end plate to the rest of the muscle fiber but that the effects are directly on the muscle membrane away from the motor end plate or upon the contractile unit of muscle.

This laboratory has attempted to produce "myasthenic" animals for testing purposes by the chemical administration of these compounds. This has not been successful to date and these investigators are now turning to animals in which thymic tumors may be induced. These mice will now be tested for the presence of subliminal neuromuscular block. Finally, these investigators are doing another closed crossed circulation procedure in which the blood of the leg of the donor animal may be used to profuse one leg of the recipient animal. After appropriate manipulation of blood and tissue cholinesterases in the two animals, recording from both legs of the donor animals will give a direct comparison of the roles played by the two types of cholinesterase compounds.

In the Laboratory of Applied Biophysics with the cooperation of Mr. Robert Bradley and Mr. Bill Matthews, the following projects are continuing. Investigations are underway for localization of cerebral tumors by isotopic detection. The main isotopes used are Zn^{69} and I^{131}. After injection into the patient, a continuous scanning of the head is undertaken with a three inch scintillation crystal. The photons so presensitized go by way of a photomultiplier tube and a preamplifier to a pulse-height analyzer. From here the recording is taken three ways. First, it may go to a standard scaler which activates a mechanism recording system. Second, it is taken into a Brown potentiometer in which the sensitivity may be altered by varying resistances. Third, from back of the Brown potentiometer leads may be taken through a condenser coupled amplifer to two neon light which in turn sweep over an infrared film. By this method approximately 80% of gliomas have been localized. Difficulties in the future are likely in two areas -- first, in the practical columnating device. The present columnator was devised by the Oak Ridge National Laboratory for a point source. The loss in sensitivity to low energy isotopes is approximately 100. If high isotopes are used, however, columnation is not obtained. We are therefore building a columnator for a sensitive volume which will be built of gold and weigh approximately 60 pounds. After the completion of the practicality of the experiment, the gold will be remelted and returned to the U. S. Mint. The second is increase of sensitivity by the detecting device and we are obtaining a new photomultiplier

tube which gives a gain of 10^{11} instead of 10^{9}. It is hoped with this that the majority of tumors may be detected and localized at a given level within the brain.

In the 1955 report, one of these investigators reported the completion of an Atlas of Muscle Disease and Neuromuscular Disorders. Much difficulty has been encountered, however, in color print reproduction, but it is anticipated that the Atlas will be published within the next three months. Work now in diseased muscle must be directed to histochemical and ultramicroscopic techniques in diseased muscle. Three phases will be attempted: the first is the electromicroscopic changes of diseased muscle with the cooperation of Dr. Wanko; second, is the utilization of specific fluorescing antibodies to myosin with the cooperation of Dr. Klatzo; and third, a continuation of the previous work on phase microscopy on fresh muscle removed by biopsy specimens.

The studies of gamma globulin in certain degenerative disorders as cerebellar ataxia are now continuing in two laboratories. That phase undertaken by Dr. Curtis as described above by use of enzyme kinetics. The Section of Biophysics will continue by the utilization of labeled alpha^{2} globulin with specific materials such as Cu^{64} and comparing the rate of appearance in spinal fluid and disappearance in blood. Finally, this Section will continue the work initiated by Doctors Li, Shy and Wells on microelectrode recording of single muscle fibers with intracellular glass electrodes. It is expected in the current year to apply this technique to man and in particular to patients with myasthenia gravis in order to record resting membrane potentials and end plate potentials in diseased states. This is a tedious technique and results should not be expected for at least three years.

AWARDS, RECOGNITIONS, AND ACTIVITIES

Staff Appointments to Universities:

Doctor G. Milton Shy, Associate Clinical Professor of Neurology, Georgetown University

Doctor Maitland Baldwin, Associate Clinical Professor of Neurosurgery, Georgetown University

Doctor Donald B. Tower, Associate Clinical Professor of Neurology and Associate Professor of Biochemistry, Georgetown University

Doctor Cosimo Ajmone-Marsan, Instructor in Clinical Neurology, George Washington University

Doctor James F. O'Rourke, Instructor in Ophthalmology, Georgetown University

Hospital Consultants:

Doctor G. Milton Shy, U. S. Medical Naval Center, Bethesda, Maryland

Doctor Maitland Baldwin, U. S. Medical Naval Center, Bethesda, Maryland

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 88 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LAB., BRANCH, OR DEPT.

4. Neurological Disorders Service
SECTION OR SERVICE

5. -
LOCATION (IF OTHER THAN BETHESDA

6. Physiology and Pharmacology in Myasthenia Gravis
PROJECT TITLE

7. G. Milton Shy
PRINCIPAL INVESTIGATOR

8. Choh-Luh Li, Richard L. Irwin, Jay Wells
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN N.I.H.) -

10. PROJECT DESCRIPTION (N-2-016)

Objectives: Recent evidence shows the pathology of myasthenia gravis to probably now lie in (1) altered motor end plates; (2) some type of circulating substance, either curareform or depolarizing; (3) a block in release of acetylcholine. Newer techniques are now available to allow further research to differentiate these three systems.

Methods Employed: The methods employed will be those combined in NINDB 8 and NINDB 1. This will consist of intrafiber recordings with microelectrodes in single muscle fibers of afflicted muscles in myasthenic man. The utilization will be half micra glass pipettes filled with .3 molar Kcl attached by way of a cathode follower system to appropriate amplification units.

Major Findings: Within the past year Dr. Li, Dr. Fatt, Dr. Shy and Mr. Wells have been able to record for the first time motor end plate potentials in vivo in the frog and rat. They have, in addition, in in vivo preparations done studies as to the origin and physiological properties of spontaneous denervation activity within single muscle fibers in vivo. This now makes possible the introduction of microelectrodes within muscle of man. Difficulties encountered, however, are the large range of resting potentials due to many and assorted technical problems, such as tip potential, injured fibers, etc. Running concurrently with this has been a pharmacological study of the depolarizing agents on myasthenic patients in which in some (i.e. 15 per cent) improvement has been found upon the administration of hexamethonium.

Proposed Course of Project: The projective research will involve the attempt at measurements of minute action potentials as recorded by microelectrodes in isolated muscle in the myasthenic muscle of man. A decrease of such minute potentials would, according to Dr. Fatt-Katz theory, indicate a decrease in release of bundles of acetylcholine. 2. To record over a large series of fibers the resting potential before and after the administration of depolarizing agents in normal man and animals and compare to myasthenic man. This is an extremely tedious and difficult technique and it is not visualized that any results will be obtained of significant quantity for statistical assessment for at least three years. Dr. Li will continue his studies (see project # 48) in animals and Mr. Wells will continue his pharmacological studies with Dr. Irwin in animals (see project #106).

Significance to Neurological Research: This is the only logical way, with known technical advances, to find the site of the disorder in the myasthenic patient.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 88 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57 $18,800	5,152	$ 53,952	3	2	5
BUDGETED POSITIONS			PATIENT DAYS		
PROF	OTHER	TOTAL			
FY'57 3	2	5			

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSIST-	[ ]
BIOLOGIC STANDARDS	[ ]	ANCE	

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Hornors, Awards & Publications 15. NINDB 88 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Some Properties of Denervated Muscle Recorded from Intracellular Electrodes" By Li, C.L., Shy, G.M., and Wells, J. Accepted for publication in Journal of Physiology, 1956 or early 1957.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 89 (C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LAB., BRANCH, OR DEPARTMENT

4. Neurological Disorders Service
SECTION OR SERVICE

5. -
LOCATION (IF OTHER THAN BETHESDA)

6. Histopathological Investigations of Neuromuscular Disorders
PROJECT TITLE

7. G. Milton Shy and Theodor Wanko
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN N.I.H.).

10. PROJECT DESCRIPTION

Objectives: To determine some of the basic anatomical and physiological changes of single muscle fibers in disease.

Methods Employed: As noted in the project sheets of 1955, the initial phase of this study was completed in the formation of an Atlas of Muscle Disease in Neuromuscular Disorders. Such an atlas will form the first basic pathological control for further studies. At the present time, it is now the desire to enter further into the following fields: 1. Electron microscopy of diseased and normal muscle, which will be done in collaboration with Dr. Wanko and his unit. This will be accomplished by minute injections of osmic acid in vivo and subsequent removal for microscopic preparations. Sections will be made with glass microtomes and studied under the electron microscope at 1/400 micron. 2. In addition to standard histochemical methods now

Methods Employed (Cont'd.): available, such as PAS stain, Gomeri Trichrome, etc., it is hoped with the collaboration of Dr. Klatzo of the Section of Neuropathology to enter into further studies by means of tagged antibodied myosin, and to study such structures under polarized and ultraviolet monochromatic radiation. 3. A study of phase microscopy of fresh muscle removed from biopsy specimens. At the present time, one of the intriguing aspects of this is the startling appearance of the so-called sarcosomes which are not readily present or apparent on optical microscopy.

Patient Material: Approximately 400 cases of muscular dystrophy are now available for this study. **(N-2-401)**

Major Findings: Work upon the atlas of microscopic histopathology of these diseases has progressed over the past year and is now entering its final stages. Much work had to be done on the colored plates in that there were approximately 80 of these in which minor variations in color becomes important in interpretation. It is anticipated that the completed atlas will be published by E. & S. Livingstone at Edinburgh in the next three months. Conclusions of histopathology of muscle are the same as those published in the 1955 report and it is too early at this time to anticipate conclusions in the three fields of further investigation.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 89 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$35,000	5,152	$40,152	2	2	4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	2	4	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards & Publications 15. NINDB 89 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Atlas of Muscle Pathology of Neuromuscular Disease" By Shy, G.M., Alvord, E.C., Berg, L., and Greenfield, J.G.

"Diseases of Muscle". A chapter in textbook by Frances M. Forster on Treatment of Neurology, by Drager and Shy. To be published by Mosby & Co. 1956.

"A New Congenital Non-Progressive Proximal Myopathy" By Shy, G.M. and Magee, K. To appear in the next issue of Journal Brain, 1956.

"Paramyotonia Congenita -- A Distinct Genetic Anatomic and Physiological Abnormality" By Shy, G.M., Drager, G., and Hamill, J. (In preparation)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 90 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Neurochemical Studies on Patients with Phenylketonuria and Galactosemia.
PROJECT TITLE

7. Dr. Anatole S. Dekaban and Dr. Donald B. Tower
PRINCIPAL INVESTIGATORS

8. Mr. Edmund Peters, Dr. William C. Curtis, and one other (to be appointed)
Dr. C. Ajmone-Marsan, Dr. Louis Sokoloff (NIMH) and Dr. Herman Kalckar(NCI)
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

Studies on Uridine Coenzymes and Galactose metabolism (Dr. Kalckar)
Studies on Phenylalamine and Tyrosine metabolism (Dr. Udenfriend)

10. PROJECT DESCRIPTION

(a) Objectives: To attempt to define the bases for the neural dysfunctions associated with phenylketonuria and galactosemia.

(b) Methodology: Development of specific approaches will depend upon the direction indicated by preliminary studies. Standard methods for determinations of the pathognomic metabolites in phenylketonuria (serum phenylalamine, urinary phenylpyruvic acid and phenolic compounds) and galactosemia (serum galactose, red cell phosphogalactose-uridyl-transferase) will be set up in order to follow clinical progress of patients studied. Electroencephalographic studies in each case are contemplated to observe effects of excess phenylalamine or galactose metabolites on EEG abnormalities in phenylketonuria and in galactosemia respectively. Cerebral blood flow, oxygen and glucose utilization studies will be carried out by the Kety-Schmidt technique to determine whether glucose oxidation by brain is impaired in these diseases (untreated).

The toxicity of various phenylalanine and galactose metabolites to experimental fetal and neonatal animals will be investigated, preferably on those species whose degree of neo-natal cerebral development is close to that of man.

(c) Patient material: Patients will be admitted to the ward service of the Section of Developmental Neurology (Dr. Dekaban). Galactosemic patients will be provided by Dr. Kalckar (NIAMD). (N-9-805)

(d) Major Findings: None. This project will be initiated in Calendar 1957.

(e) Significance to Neurological Research: Both phenylketonuria and galactosemia are metabolic diseases due to genetic defects in a respective enzyme necessary to normal metabolism of dietary phenylalanine or galactose. The biochemical abnormalities are known in detail and the genetics of both are clear. However, the bases for the neural toxicity, primarily severe mental retardation and seizures (questionable for galactosemia) are completely unknown beyond the fact that it is closely related to ingestion of phenylalanine or galactosemia, since dietary restrictions are attended by remission of biochemical and clinical abnormalities. Phenylketonuria is estimated to have an incidence of 1:10,000, a not inconsiderable portion of mentally defectives. The incidence of galactosemia is unknown, but Kalckar believes it may not be as rare as once thought. Not only is it of importance to elucidate the mechanisms of neural toxicity in these diseases, but a clearer understanding of factors which produce mental retardation is of utmost importance to the problems of cerebral palsy and mental disease in general.

(f) Proposed Course: To initiate the above studies.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 90 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW AND APPROVAL ☐ PROFESSIONAL AND TECHNICAL ASSISTANCE ☐

BIOLOGIC STANDARDS ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

Dr. Herman Kalckar-Laboratory of Biochemistry and Metabolism(NIAMD)
Dr. Louis Sokoloff-Section on Cerebral Metabolism (NIMH)
Dr. Sidney Udenfriend-Laboratory of Chemical Pharmacology(NHI)

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications 15. NINDB 90 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - -NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 91 (C)
SERIAL NUMBER

2. NIMH and NINDB
INSTITUTE OR DIVISION

3. Lab Research(NIMH)- Medical Neurology (NINDB)
LABORATORY, BRANCH, OR DEPARTMENT

4. Section on Cerebral Metabolism (NIMH)
Section of Clinical Neurochemistry (NINDB)
SECTION OR SERVICE

5. _____
LOCATION(IF OTHER THAN BETHESDA)

6. The Cerebral Circulation in Minor Seizures and the Effects of Hyperventilation Thereon.
PROJECT TITLE

7. Dr. Louis Sokoloff (NIMH) and Dr. Donald B. Tower (NINDB)
PRINCIPAL INVESTIGATORS

8. Dr. Charles E. Wells, Dr. W. King Engel and Dr. C. Ajmone-Marsan (NINDB)
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

10. PROJECT DESCRIPTION

(a) Objectives: To measure cerebral blood flow in patients with minor cerebral seizures (petit mal type) during control, hyperventilation and seizure periods.

(b) Methodology: Cerebral blood flow studies will be performed, using the radioactive krypton (Kr^{79}) method devised by Lewis, Sokoloff, Wentz, Wechsler and Kety (Fed. Proc. 14: 92 (1955)) and used extensively by Dr. Sokoloff during 1954-55 at the U.S. Naval Air Development Center, Johnsville, Pa.

Concentrations of radioactive Kr^{79}, not exceeding 100 $\mu c./L.$ will be breathed by the subject from a closed spirometer reservoir through a tightly fitting mask for a period not exceeding 20 minutes. Readings over the cerebral hemispheres with an extensively shielded scintillation counter will be possible about every 30 seconds.

Simultaneously arterial and cerebral venous blood samples will be drawn for Kr^{79} content. From these data and the Fick principle, cerebral blood flow can be calculated.

Cerebral blood flow will be determined by this method in the resting (control) state, during hyperventilation and during seizures induced by hyperventilation, photic stimulation or other suitable means. Whenever possible simultaneous electroencephalograms will be recorded. Arterial and cerebral venous blood samples will also be analyzed for pCO_2, CO_2 content, pH, oxygen saturation and glucose during these studies.

(c) Patient Material: Patients with suitable seizures and activation response to hyperventilation and/or photic stimulation will be admitted to NINDB wards for this study. **(N-1-510)**

(d) Major Findings: None. The project has been approved by the N.I.H. Radiation Safety Committee. It has been impossible to implement this project so far due to (1) limitations on Dr. Sokoloff's time imposed by prior committments to other existing projects and (2) lack of suitable patient material - only one being available in 1956 and this one could not be studied due to the above reason.

(e) Significance to Neurological Research: The nitrous oxide method for measurement of cerebral blood flow requires a 10 minute period of observation for obtaining an average flow per minute during this period. From studies by this method it is known that hyperventilation in normal subjects and in patients with generalized seizures during the interictal period results in decreased cerebral blood flow and that generalized seizures induced in monkeys result in markedly increased cerebral blood flow. No studies have been reported on effects of hyperventilation in patients with minor seizures (petit mal type), although it is in this group that greatest susceptibility to the ictogenic effect of hyperventilation is encountered. In addition the relationships between cerebral blood flow and seizures has not been studied during actual seizures in man because of the time limitation imposed by the nitrous oxide method. With the radio-krypton method accurate recording of such data would be of fundamental significance.

(f) Proposed Course: To carry out such studies as soon as suitable patients become available.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 91 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY' 57			0			0
	BUDGETED POSITIONS			PATIENT DAYS		
	PROF	OTHER	TOTAL			
FY'57						

13: BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

N.I.H. Radiation Safety Office.
Massachusetts Institute of Technology - Cyclotron production of Krypton^{79}.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB 91 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Wells, C. E.: Chronic Hypoventilation in an Epileptic Patient. Neurology, 6: 744-49 (1956).

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956;

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 52 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Characteristics of Isocitric Dehydrogenase and other Krebs Cycle Enzymes in Cell Fractions of Cerebral and Hepatic Tissue
PROJECT TITLE

7. Dr. James A. Shepherd (PHS Post-doctoral Fellow).
PRINCIPAL INVESTIGATOR

8. Mr. Edmund Peters, Dr. Donald B. Tower, Dr. William C. Curtis, one other (to be appointed) and Dr. Henry McIlwain (NINDB Consultant, 1957).
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objectives: To study intimate enzymatic characteristics of isocitric dehydrogenase in isolated cell fractions of cerebral tissues and to compare them with those of the comparable liver enzyme.

(b) Methodology: Cerebral and hepatic tissue cells will be disrupted sonically, fractions isolated by differential high speed centrifugation, and enzyme activity determined after incubation with citrate by spectrophotometric determination of the DPN → DPN H_2 reaction coupled with citrate → isocitrate reaction of the enzyme. Activities of the enzyme in various individual cell fractions (total, mitochondrial, microsomal, supernatent and nuclear) and combinations of two or more will be determined, referred to protein nitrogen contents, and correlated with infractionated activity of whole cell. Physico-chemical separation and characterization

(c) Major Findings: Previous work by the principal investigator elsewhere has confirmed in rabbits the report of Hogeboom and Schneider for mice that the majority (82%) of the isocitric dehydrogenase of liver fractions

is associated with the soluble (supernatent) fraction. However, in fractionaction of homogenates of rabbit cerebral cortex this enzyme is equally distributed between soluble (supernatent) and sediment (mitochondrial) fractions and the sum of fraction activities was 200% of that of the original homogenate. The results seemed consistent with the presence of two enzymes. These findings raise the questions: (1) whether the soluble and mitochondrial enzymes are different or the same enzyme in different intracellular locations, and (2) whether this is a special case for cerebral tissues or for cerebral tissues of a particular species or whether measurements reflect two cell types, one with supernatent and the other with mitochondrial loci of activity.

(d) Significance to Neurological Research: Enzymes of the Krebs cycle are key enzymes in the fundamental energy metabolism of the neuron. An understanding of their characteristics, mechanisms of action and cellular location is basic to neurochemical concepts of neuronal metabolism. These enzymes are also involved in metabolic steps which relate to amino acid and fatty acid synthesis and metabolism and appear to be concerned with the mechanisms underlying seizures. The initiation of this project will provide data on an interesting problem in enzymology as well as development of approaches to the study of enzymic defects in the Krebs cycle in certain seizure states such as fluoro-citrate poisoning, pyridoxine deficiency and spontaneous seizures in man, which will be necessary to obtain complete understanding of the seizure process.

(e) Proposed Course: To continue studies outlined above and in particular to prepare purified enzymes from the two fractions with equal activities per unit nitrogen and study the physico-chemical properties of each in order to answer questions posed by findings to date.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 92 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW AND APPROVAL ☐ V PROFESSIONAL AND TECHNICAL ASSISTANCE ☐

BIOLOGIC STANDARDS ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERISL NO(S):

PHS Post-doctoral Fellowship Program - Salary Support for Dr. Shepherd.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications 15. NINDB 92 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Shepherd, J. A.: "Factors influencing the determination of the intracellular distribution of isocitric dehydrogenase in rabit cerebral cortex" J. Histochem. and Cytochem. 4: 47-54 (1956)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 93 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION(IF OTHER THAN BETHESDA)

6. A Study of Abnormal Urinary Metabolites Excreted by Patients with Seizures, Cerebellar Ataxia and other Neurological Diseases
PROJECT TITLE

7. Dr. W. King Engel
PRINCIPAL INVESTIGATOR

8. Mr. Edmund Peters, Dr. Donald B. Tower and one other (to be appointed).
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objectives: To screen 24-hour urine specimens from patients with various neurological diseases, particularly seizures and cerebellar ataxia, for presence of abnormal metabolites or increased amounts of normal metabolites of the tryptophan-indole group and to determine what, if any, correlation these may have with the clinical diagnoses.

(b) Methodology: 24-hour urine samples will be collected on two non-consecutive days. Each will be screened by the Watson-Schwartz test for Ehrlich-positive compounds and aliquots of each will be investigated by two-dimensional chromatography for indole compounds and for amino acids by the methods of Jepson and Dent respectively. Routine urinalyses will be carried out on each sample, including creatine-creatinine determinations. Further runs will be made on any patient with abnormal findings. The abnormalities will be classified, and possible correlations evaluated.

(c) Patient Material: Studies will be carried concurrently with work-up of patients admitted to NINDB wards for various other projects. Specific admissions to this project may become desirable if initial results so indicate. (N-10-009)

(d) Major Findings: This project will begin in Calendar 1957.

(e) Significance to Neurological Research: In recent years a number of neurological diseases arising from biochemical abnormalities have been defined. A number of these have characteristic abnormal metabolites excreted in the urine of such patients, e.g. phenylketonuria, galactosemia, Wilson's disease, pyridoxine deficiency. The study of these urinary constituents has not only shed light on the pathological process but has clarified many facets of normal metabolism. In connection with phenylketonuria, Armstrong and co-workers have been surveying urine samples for phenolic compounds with considerable success. Seven and Markovitz (unpublished) and Remington (unpublished) have both observed Ehrlich-positive compounds, probably indoles, in urines of seizure patient. Jepson and co-workers have described a new syndrome ("H" disease) characterized by dermatitis, intermittent cerebellar ataxia, mental retardation, aminoaciduria of unique pattern (especially aromatic amino acids) and large excretion of indole-3-acetic acid and indican (Lancet, pp. 421-428, Sept. 1, 1956) and have described methods for studying these compounds by paper chromatography (Lancet, p. 1009, Nov. 12, 1955). These latter authors suggest "H" disease is a genetically determined abnormality in tryptophane-nicotinamide metabolism. It is possible that these and other disorders such as malignant carcinoid syndrome (Udenfriend) represent a family of metabolic disorders in tryptophan-micotinamide metabolism analogous to those known for phenylalanine-tyrosine metabolism. It is becoming very apparent that disorders in metabolism of these aromatic amino acids have particularly deleterious consequences for the nervous system, especially in mental retardation. The interests of NINDB in the fields of cerebral palsy, seizures, myopathies and cerebellar diseases make research into these possibilities of great practical as well as theoretical importance.

(f) Proposed Course: To implement the project.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 93 (C)
SERIAL NUMBER

12: BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$15,000	5,152	$ 20,152	1	1	2
	BUDGETED POSITIONS			PATIENT DAYS		
	PROF	OTHER	TOTAL			
FY'57	1	1	2			

13. BUDGET ACTIVITY:

RESEARCH ☒ ADMINISTRATION ☐

REVIEW AND APPROVAL ☐ PROFESSIONAL AND TECHNICAL ASSISTANCE ☐

BIOLOGIC STANDARDS ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Section on Developmental Neurology - Dr. Dekaban - consultation only.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications 15. NINDB 93 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 94 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Quantitative, Microchemical Determination of Acetylcholine in Biological Specimens
PROJECT TITLE

7. Dr. William C. Curtis and Dr. Donald B. Tower
PRINCIPAL INVESTIGATORS

8. Mr. Milton A. Pogorelskin
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH):

Dr. Sidney Udenfriend - Laboratory of Chemical Pharmacology (NHI)-fluorospectrometer.

Dr. E. C. Horning-Laboratory of Chemistry of Natural Products (NHI)-infrared spectroscopy.

10. PROJECT DESCRIPTION

(a) Objectives: To adapt and develop a specific, quantitative chemical method for the determination of acetylcholine in brain tissue and fluids.

(b) Methodology: See under major findings.

(c) Major Findings: R. Neu (Ztschr. f. anal. Chemie 143: 30-38 (1954) reported that, in the presence of tetraphenyl diboronoxide and a flavonol, as little as 0.1 μg. of acetylcholine can be deteced as a colored precipitate or as red fluorescence under ultra-violet light. Neu reported that when quercetrin was used as the flavonol, acetylcholine but not choline reacted. In attempting to adapt these findings to a method for determining acetylcholine, it was found that pure quercetrin gave no differential reaction. In checking with Neu, he discovered that a trace of quercetin in the quercetrin is required to produce a colored reaction product with acetylcholine but not choline.

With this discovery as a starting point this year, it has been found that when methanol solutions of tetraphenyl diboronoxide and either quercetrin or quercetin are added to aqueous solutions of choline or acetylcholine (as the chlorides), an orange precipiate is formed. The precipitates settle slowly and emit a reddish-orange fluorescence on exposure to ultraviolet light. The precipitates are soluble in acetone, n-butyl alcohol and ethyl acetate, partially soluble in chloroform and ether, and insolubie in hydrocarbon solvents such as benzene, toluene and hexane. When 0.1 to 2% quercetin is added to quercetrin and the reaction carried out as above, acetylcholine yields an orange precipitate which settles slowly out of solution and which emits a strong red fluorescence in ultraviolet light. This precipitate has the same solubility behavior as material obtained with either flavonol alone. Under the same conditions, choline does not yield any visible precipitate but merely a yellow coloration without ultraviolet fluorescence, which cannot be distinguished visually from the reagent blank.

Optimal conditions for carrying out this reaction for acetylcholine are as follows: 0.5 ml. of 0.5% tetraphenyldiboronoxide (freshly prepared) in methanol, 1 ml. of 0.1% flavonol in methanol and 4 ml. of pH 5.0 buffer are added to 1 ml. of aqueous acetylcholine solution. The flavonol used is 1.6% quercetin in quercetrin, the optimum ratio for the selective acetylcholine reaction. Optimum buffer concentration is from 0.125 to 2.0 N with acetate buffers superior to phosphate buffers. There is a time factor involved in the reaction which must be evaluated spectrophotometrically. Shorter wave lengths of ultraviolet light produced a more intense fluorescence than longer wave lengths.

(d) Significance in Neurological Research: Significance of this project is most important and fundamental. No satisfactory chemical method for determination of microgram quantities of acetylcholine in biological specimens has ever been developed. Bioassay procedures are tedious, somewhat non-specific and often not sufficiently sensitive. In view of the importance of acetylcholine as a peripheral and also probably as a central transmitter of nerve impulses, there is a pressing need for better assay methods. This need is reinforced by the recent development by Udenfriend of a very satisfactory chemical method for Serotonin, a probable second transmitter in the central nervous system. Positive chemical identification of acetylcholine in nervous tissue has only been reported twice in 35 years. There is need for reassessment of acetylcholine with a specific chemical method particularly as more and more possible transmitters are proposed.

(e) Proposed Course: All preliminary visual observations, usually carried out in developing a new fluormetric procedure, have been completed. Appropriate instrumentation and applications are now to be studied, including: (1) absorption spectra of all components (reagents) of the fluorescent system by Beckman DU spectrophotometer in order to predict the optimum wave length for excitation and possible interfering substances; (2) concentration factors insuring fluorescent production in a non-restricted zone of the solution, falling within the optical path of the detection instrument; (3) complete fluorescent spectra of the fluorescent system, using a red-sensitive fluorospectrometer; (4) determination in pure solutions of effects of temperature, pH, time of

exposure, trace impurities and quenching; (5) adaptation to blood, urine, cerebrospinal fluid and tissues with determination of native fluorescent spectra thereof.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data: 11. NINDB 94 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,000	5,152	$ 25,152	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Dr. Sidney Udenfriend-Laboratory of Chemical Pharmacology (NHI)- fluorospectrometer.

Dr. E. C. Horning - Laboratory of Chemistry of Natural Products(NHI) - infrared spectroscopy.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15 NINDB 94 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956.

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 95 (C)
SERIAL NUMBER

2. NINDB 3. Medical Neurology
INSTITUTE OR DIVISION LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry 5.
SECTION OR SERVICE LOCATION (IF OTHER THAN BETHESDA)

6. The Nature and Characterization of Urinary Polypeptides, Pyrogens and Similar Molecules.
PROJECT TITLE

7. Dr. William C. Curtis
PRINCIPAL INVESTIGATOR

8. Mr. John Phoenix, Dr. Donald B. Tower, and Dr. G. M. Shy
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None.

10. PROJECT DESCRIPTION

(a) Objectives of this project are to develop suitable physico- chemical methods for the isolation and characterization of oxyproteic acids, pyrogens and similar molecules. The chemical and physical natures of these compounds are poorly understood and their significance and mechanisms of action remain obscure.

(b) Methodology: Isolation and purification of oxyproteic acids from urine and of the pyrogen, Piromen, will be carried out by ion exchange, column chromatography, foam fractionation and absorption techniques. Characterization studies will employ electrophoresis, diffusion, ultracentrifugation, sedimentation, velocity and equilibrium, selective adsorption and solubility studies to provide data on molecular size and structure.

(c) Patient Material; Will not be used for this project initially except for urine specimens from NINDB patients admitted to other projects. (N-2-208)

(d) Major Findings: In preliminary experiments abnormally high concentrations of urinary polypeptides or pseudo-peptides have been isolated by both chemical and physical methods from urines of patients with muscular dystrophy. The materials isolated by the two methods exhibit the same solubility behavior and are normal urinary constituents. At present states of development physical methods of separation are not applicable to clinical investigation. However, chemical fractionation by means of barium salts can be readily employed to determine the clinical significance of the urinary polypeptides. The most satisfactory procedure

has been found to that of Lustig and Tuchler (Biochem. Z. 289:143 (1937). This procedure has been indispensible in evaluating the course of physical fractionations.

Three significant findings have come to light. (1) The urinary barium fraction is composed of highly surface active and foam-producing constituents. It is possible that a simple relationship can be established between the foaming properties of urine and their polypeptide content. Foaminess of urine is one of its characteristic physical properties. Purification of the urinary barium fraction may be more easily accomplished by foam fractionation than by the involved chemical fractionation now used. (2) The major portion of urinary polypeptides can be quantitatively adsorbed on activated charcoal, alumina or ion exchange resins. This implies the possibility of adapting chromatographic adsorption for quantitative determination and chemical differentiation of these materials. (3) Preliminary experiments with a commercially available molecular filter clearly demonstrate that a suitable apparatus of this type would greatly facilitate the isolation of polypeptides for clinical investigation from not only urine but also other biological fluids such as serum.

(e) Significance to Neurological Research: This study is designed to shed some light on the nature and signficance of certain complex molecules. Polypeptides occur normally in urine as products of in vivo degradation of proteins, especially albumen. No detailed study or characterization of these compounds has ever been reported. In neuromuscular diseases there is degradation of nerve and muscle tissue, apparently associated with increased excretion of polypeptides in the urine. In muscular dystrophy injected human serum albumen tagged with I^{131} there is evidence for abnormal loss or metabolism of such albumen. A comparison of excretions by normal subjects and by patients with muscle disease in terms of quantity and types of polypeptides would be of considerable significance. In a more fundamental sense these studies may have an important bearing on the general problem of protein metabolism, particularly its catabolic aspects.

(f) Proposed Course: To continue studies on the above problems outlined under Major Findings.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

Part B: Budget Data 11. NINDB 95 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57						

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Clinical Investigations Division, NINDB-Dr. Shy (Serial No._____).

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards and Publications 15. NINDB 95 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 96 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Physico-chemical Studies of Human Cerebrospinal Fluid Proteins in Demyelinizing Diseases.
PROJECT TITLE

7. Dr. William C. Curtis
PRINCIPAL INVESTIGATOR

8. Mr. John Phoenix, Mr. Edmund Peters, Dr. Donald B. Tower, one other (to be appointed), Dr. Charles E. Wells and Dr. W. King Engel.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH)

None.

10. PROJECT DESCRIPTION

(a) Objectives of this project are to study the abnormalities in the protein fractions of cerebrospinal fluids from patients with multiple sclerosis in order to determine the significance of such abnormalities both diagnostically and prognostically in the clinical course of the disease.

(b) Methodology: See 1955 report (Serial NINDB-15(c) and major findings.

(c) Patient Material: See 1955 report (Serial NINDB-15(c). (N-10-007)

(d) Major Findings; in approaching this problem it has been obvious that certain protein chemical and physico-chemical techniques would have to be adapted and perfected before fractionation and characterization of blood and spinal fluid gamma globulins could be undertaken. To this end, some fairly stable, physiologically active protein needed to be selected for use in standardizing prospective protein techniques. Studies on guinea pig serum L-asparaginase (developed for another project (Serial No. NINDB 97 (C)) have shown that this protein, a globulin, is particularly adapted to this purpose. Hence, the isolation, purification and evaluation of the enzyme kinetics of L-asparaginase have been undertaken.

The first phase of this study has been completed with the exception of a few minor details. Electrophoretic and ultracentrifuge characterizations of the isolated crude enzyme (10-fold purification) have indicated two contaminants. Optimal conditions and methods for this initial isolation and for enzyme assay have been established. Enzyme kinetics of the partially-purified enzyme have been completed. The second phase, involving purification of the crude enzyme by chromatographic and foam fractionation techniques has been initiated. During the course of the preliminary studies, it has been found that the enzyme protein can be completely adsorbed on modified cellulose and on carbon dioxide foam.

It is felt that the use of a globulin with easily assayed enzymatic activity represents a valuable tool for the perfection of appropriate techniques, since the preservation of enzymatic activity serves as an important indicator of protein integrity. The lack of such a convenient indicator in gamma-globulins makes their study more difficult and requires development of techniques which can be demonstrated to accomplish this end with similar suitable protein molecules.

(e) Significance to Neurological Research: It is self evident, since it represents a detailed study into an established chemical abnormality in a disease, multiple sclerosis, which is a major problem not only from a public health standpoint but from a diagnostic, prognostic and therapeutic standpoint. Nothing is known about its course or the mechanisms underlying its cause. With this first clue of biochemical abnormality a step in the direction of covering these many problems can be made by such a detailed and long-term approach.

(f) Proposed Course; Perfection of methods applicable to isolation of gamma globulin fractions from cerebrospinal fluid (and serum) by suitable physical methods such as foam fractionation, selective adsorption, counter-current distribution, electrophoresis-convection and/or column electrophoresis. Since it is not feasible to obtain sufficient gamma globulin to carry out the preliminary phases of these studies nor to ensure maintenance of protein integrity without a suitable indicator, L-asparaginase from guinea pig serum will be utilized for these purposes.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 96 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,000	5,152	25,152	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.1	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications 15. NINDB 96 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 97 (C)
SERIAL NUMBER

2. NINDB
INSTITUTES OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinucal Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Metabolism of Glutamic and Aspartic Acid Amides in Vivo.
PROJECT TITLE

7. Dr. William C. Curtis and Dr. Donald B. Tower
PRINCIPAL INVESTIGATORS

8. Dr. Charles E. Wells, Dr. W. King Engel and Mr. John Phoenix
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO(S)S IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objectives; Are to develop suitable clinical methods for simultaneous quantitative determination of glutamic acid, aspartic acid, glutamine and asparagine in body fluids (blood, cerebrospinal fluid, urine) in order to follow the metabolic fate of ingested doses of glutamine and asparagine or both in seizure patients on such therapy and to correlate such findings with oral dosage and clinical response.

(b) Methodology: Se Major Findings.

(c) Patient Material: Will be derived from the patients being studied in the clinical study assessing the anticonvulsant effectiveness of glutamine and asparagine (Serial # N-1-200). Other NINDB patients not on such therapy will be used for acute studies.

(d) Major Findings: Difficulties in the reproducibility of the dinitrophenyl-amino acid column chromatographic method developed in 1955 have been encountered. These reside in the conditions necessary for quantitative conversion of the amino acids to their dinitro-phenyl derivatives. It now develops that similar difficulties have been encountered with all other workers using this method, despite previous published reports to the contrary. Accordingly, because of the great potential value and current widespread use of this procedure, considerable effort has been expended in modifying the procedure to yield quantitative,

reproducible conversions. A micro reaction cell has been designed and constructed (with assistance of the NIH Instrument Shop) with specially designed micro-electrodes and platinum stirrer. Preliminary trials indicate that this apparatus will function as desired but the time required for its construction has precluded any full experiments this year.

An alternative study was meanwhile undertaken, using the guinea pig serum asparaginase enzyme described by Meister. Preparation and purification of the enzyme according to Meister's procedure has been satisfactory and reproducible. A procedure for serum, cerebrospinal fluid and urine asparagine assays has been developed and used successfully on a number of patient samples. Peak serum levels of 0.5 to 0.8 μM/ml. have been obtained, similar to those obtained by the dinitrophenyl-column method and by another procedure developed in Baltimore by Van Buskirk and Bessman. The serum values reach a peak usually at 1 hour after oral asparagine doses and return to control values at 3 to 4 hours. Little, if any, asparagine is detectable in cerebrospinal fluids at any time, as followed by serial samples after catheterization of the lumbar subarachnoid space. 24-hour urinary excretion of asparagine does not exceed normal values obtained here and reported by Moore and Stein, indicating that assimilated asparagine is all metabolized and not excreted as such.

The lack of sufficient amounts of C^{14}-asparagine has made it impossible to follow its metabolism in monkeys in vivo as planned. Supplies are now on hand for this study.

The initiation of clinical studies with 2-pyrrolidinone and γ-aminobutyrate as possible anticonvulsants has necessitated development of methods for their detection. It is anticipated that the dinitrophenyl derivative of γ-aminobutyrate can be formed and isolated for quantitation by column chromatography. This method has not been implemented pending studies on this general method outlined above. A method for determining 2-pyrrolidinone has been successfully worked out. It was found that published methods involving hydrolysis to γ-aminobutyrate were inconstant and not quantitative. However, conversion of the compound to the 2-thio derivative in the presence of P_2S_5 in xylene was found to be rapid and quantitative. Determination of the 2-thio-derivative with oxidized sodium nitroprusside spectrophotometrically at 585 mμ could then be readily carried out. Serum levels of 2-pyrrolidinone after oral ingestion of 1 mM/kg. doses have been of the order of 1.0 μM./ml. with a peak value at 30-60 minutes, indicating rapid absorption and distribution of the compound. No spinal fluid studies have been done so far.

Incidental to the foregoing studies, the pharmacological properties of 2-thiopyrrolidine have been under investigation in cooperation with Dr. R. L. Irwin (Section of Clinical Neuropharmacology NINDB). Definite sedative or tranquilizing properties were observed in mice, rats and cats. These studies are being continued by Dr. Irwin as a separate project (see NINDB Serial # 108).

One of the extramural clinics cooperating in asparagine studies has confirmed results obtained at NINDB. Drs. Van Buskirk and Bessman (Baltimore) have obtained comparable serum asparagine levels by a modification of the Prescott-Waelsch procedure for glutamic acid. In addition these investigators have indications that assimilation of asparagine promotes glutamine production (presumably by the following sequence:

$$\text{Asparagine} \rightarrow \text{Aspartic Acid} + NH_3$$

$$\downarrow$$

$$\text{Oxaloacetic Acid} + NH_3$$

$$NH_3 + \text{glutamic acid} \rightarrow \text{glutamine}$$

which probably occurs in the liver. Note that some NH_3 is also incorporated into urea, as evidenced by elevated BUN levels in patients on asparagine or glutamine therapy). Their most interesting finding is that, while usually no change in blood ammonia levels occur following asparagine ingestion (confirmed by NINDB studies), in patients who exhibit severe nausea and vomiting on asparagine ingestion elevated serum ammonia levels are found. The implication is strong that a correlation may exist between these two events.

(e) Significance to Neurological Research: Significance of this project is in the interpretation of results being obtained in clinical therapy with glutamine and asparagine. With the use of any new compound for therapy it is important to be able to determine it in body fluids, to know the course of its metabolism and to be able to correlate dose, body level and clinical effect. With the quantities of amides being administered this becomes even more important.

(f) Proposed Course: To continue the above studies with emphasis on completion of the dinitrophenyl-amino acid column chromatographic method and its application to body fluid and tissue amino acid analyses and specifically to determination of γ-aminobutyrate; and to initiate *in vivo* studies of asparagine metabolism with C^{14}-asparagine.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 97 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,000	5,152	$25,152	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH [X] ADMINISTRATION [ ]

REVIEW AND APPROVAL [ ] PROFESSIONAL AND TECHNICAL ASSISTANCE [ ]

BIOLOGIC STANDARDS [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications 15. NINDB 97 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Tower, D. B.; "The Status of the Medical Treatment of Seizures," in Williams, D. (Ed.): Modern Trends in Neurology (2nd Ser.) London, Butterworth's, In Press.

Hawkins, J.E. and Tower, D. B. "The use of methyl-ethyl-glutarimide (Megamide) in screening anticonvulsant compounds and the anticonvulsant potency of gamma-aminobutyric acid and 2-pyrrolidinone." Proc. Soc. Exp. Biol. and Med. In Press.

The following are in Preparation from one of the cooperating clinics: Baldwin, R., Bessman, S. and Van Buskirk, C. "The Effect of asparagine on the blood ammonia content"

Baldwin, R., Van Buskirk, C. and Bessman, S. "The Toxicity of asparagine as an effect of increased blood ammonia."

Bessman, S. Van Buskirk, C. and Baldwin, R. "The interrelation of asparagine and glutamine in the human."

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. **NINDB 98 (C)**
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION(IF OTHER THAN BETHESDA)

6. Clinical Evaluation of the Value of Glutamine and Asparagine for the Clinical Control of Seizures.
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Charles E. Wells, Dr. W. King Engel and Dr. C. Ajome-Marsan.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objectives: Are to study the effectiveness of two naturally-occurring amino acid amides, L-asparagine and L-glutamine, in controlling seizures in epileptic patients and to observe their effects on epileptiform activity in the electroencephalogram of suitable patients. This project had its inception in the findings on human epileptogenic cortex in vitro that significant, chronic defect in metabolism of acetylcholine, glutamic acid and electrolytes occur which can be reversed by addition in vitro to such tissue of either glutamine or asparagine, neither of which appear to affect normal in vitro metabolism nor to exhibit any effects when administered in large quantities in vivo to normal subjects.

(b) Methodology and Patient Material: See 1954 project report (NINDB-16(C)). (N-1-200)

(c) Major Findings: Over 50 patients have now been admitted to this project at NINDB and another 200 have now been studied by clinics and cooperating physicians in the extra-mural phases of this program (See Item 14 below). A preliminary conference of all investigators concerned was held on Feb. 22, 1955 to assess progress. The opinions of the conferees can be summarized as follows:

Percentage significantly improved by asparagine	-	40
Percentage not benefitted	-	50
Percentage with increased seizure activity	-	10
Percentage with EEG improvement	-	25
Percentage with severe side reactions	-	15

The conferees felt that on the basis of results at that time, most of which had been obtained on severely involved patients, that asparagine represented an effective anti-convulsant agent in this difficult group. Additional study was voted through calendar 1956 in order to permit longer term evaluation, to assess responses of various types of seizures, to compare efficacy of asparagine alone with other anti-convulsants, and to complete various ancillary studies on blood levels, psychometric evaluations and the like. It was the opinion of the group that, under present circumstances of cost and bulk of the preparation, asparagine probably could not compete effectively with established anti-convulsants despite its demonstrated therapeutic value. It was agreed to hold a final conference early in 1957 to compile results of the study for publication. The value of this project in defining many factors of anticonvulsant therapy evaluation has been obvious and should contribute much to studies on future agents.

From the studies at NINDB and one cooperating clinic (Dr. Van Buskirk-Baltimore), it is obvious that asparagine (or glutamine) is rather inefficiently utilized. Blood levels have in general been low (about 0.5 μM/ml. maximum) and detection of asparagine in cerebrospinal fluid has been difficult. The majority of the dose appears to be siphoned off by liver, kidney and other tissues before adequate concentrations can penetrate the central nervous system compartment. This may account at least in part for the lack of efficacy in some patients. Preliminary data of Dr. Van Buskirk's group suggest that the untoward side-effects encountered in a few patients may relate to increases in blood ammonia after asparagine dosage, an increase not seen in the majority of patients so treated. Studies by this group also suggest that increased synthesis of glutamine may be stimulated by the large amounts of asparagine being ingested. Confirmation of these observations will be sought by studies at NINDB now under way.

As a result of the foregoing, plus the experimental data obtained by the Research Division of Merck and Co. on gamma-aminobutyrate and its lactam, 2-pyrrolidinone, indicating potent anticonvulsant activity for these two compounds, a modification of the NINDB project has begun. Patients now on asparagine and suitable new patients are being started on 2-pyrrolidinone or γ-aminobutyrate in order to assess their clinical efficacy. Preliminary results since initiating this study in September 1956 have been encouraging. 2-pyrrolidinone has several potential advantages over asparagine or glutamine. It is a liquid of S.G. 1.1, it is commercially available in crude form and easily purified, and it is very inexpensive. Doses of the order of 1 to 2 mm/kg. (0.2 ml.) appear to be effective and satisfactory blood levels have been obtained. It is so far without untoward side effects (gastro-intestinal) encountered with asparagine and is readily assimilated. Experimentally it has a longer duration of action on animals exposed to convulsants and it appears to be readily converted by tissues to its active form, γ-aminobutyrate. The possibility that the latter ability may vary from patient to patient indicates the desirability of complementing these studies by clinical evaluation of γ-aminobutyrate as well. Such studies are now under way.

(d) Significance in Neurological Research: This would seem to be self-evident.

It represents a new type of compound which has definite anticonvulsant properties, but which differs from all other anticonvulsants not only in its chemistry but in its lack of toxicity and lack of sedative or hypnotic action. It represents development of therapy based on a demonstrated biochemical lesion in human epileptogenic brain tissue. The number of problem cases referred to NINDB or contained in inquiries from neurologists and physicians in this country and abroad indicate that better, more effective therapy for seizures is in demand. With over a million and a half seizure patients in this country alone, it is a major health and economic concern. In addition this project is representative of the type of research for which the clinical investigation phases of NIH were created in that it has taken laboratory findings, applied them to patient material at the Clinical Center in a detailed manner seldom possible elsewhere, developed agents of considerable initial cost to the point where cost is being lowered to more reasonable ranges, and promoted trials elsewhere.

(e) Proposed Course: To complete evaluation of asparagine and report results. To continue evaluation of 2-pyrrolidinone and γ-aminobutyrate along the lines indicated.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 98 (C)
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			.5	.5	1.
#20,000	5,152	25,152			

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH IN DICATE SERIAL NO(S):

(a) Extra-mural grants, coordinated by Section of Clinical Neurochemistry, for assessment of L-asparagine in seizure therapy on approximate 100 patients to:
Harvard Medical School (Children's Medical Center)
University of North Carolina Medical School
University of Buffalo Medical School
University of Maryland Medical School
University of Virginia Medical School

(b) Cooperative studies with Section of Clinical Neurochemistry for individual cases by:
Dr. William Caveness - College of Physicians & Surgeons, N. Y.
Dr. Denis Williams - National Hospital, Queens Square, London, England

Dr. Irwin Levy - Washington Univ. Medical School
St. Louis, Mo.
Dr. Hudson Hoagland - Worcester Foundation, Worcester, Mass.
Dr. Saul Korey - Western Reserve Medical School,
Cleveland, Ohio.
Dr. Louis Goodman - Univ. of Utah Medical School

(c) Research and Development Divisions, Merck & Co., Inc.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15 NINDB 98 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Tower, D.B. "The Neurochemistry of Seizures", pp. 169-197 in Korey, S.R. and Nurnberger, J.I. (Eds.): Progress in Neurobiology I. Neurochemistry. New York, Hoeber, 1956.

Tower, D.B.: "Neurochemical Aspects of Pyridoxine Metabolism and Function," Am. J. Clin. Nutrition, 4: 329-345.

Tower, D.B.: The Status of the Medical Treatment of Seizures" in Williams, D. (Ed.): Modern Trends in Neurology (2nd Ser). London, Butterworth's, In Press.

Hawkins, J. E. and Tower, D. B.: "The use of methyl-ethyl-glutarimide (Megamide) in screening anticonvulsant compounds and the anticonvulsant potency of gamma-aminobutyric acid and 2-pyrrolidinone." Proc. Soc. Exp. Biol. and Med. In Press.

The following are in preparation from one of the cooperating clinics:

Baldwin, R., Bessman, S. and Van Buskirk, C. "The effect of asparagine on the blood ammonia content".

Baldwin, R., Van Buskirk, C. and Bessman, S. "The toxicity of asparagine as an effect of increased blood ammonia."

Bessman, S., Van Buskirk, C. and Baldwin, R. "The interrelation of asparagine and glutamine in the human."

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 99 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Investigation of Vitamin B_{12} Levels in Cerebrospinal Fluid
PROJECT TITLE

7. Dr. Charles E. Wells
PRINCIPAL INVESTIGATOR

8. Dr. Guenther R. Haase, Dr. W. King Engel and Dr. Donald B. Tower
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objective: To determine cerebrospinal fluid levels of Vitamin B_{12} in health and various diseases and to determine whether the vitamin, when given in large doses, is concentrated in the cerebrospinal fluid compared to blood serum.

(b) Methodology and Patient Material: Initial samples were assayed by the Research Division, Merck and Co., Rahway, N.J. Results of these assays were sufficiently encouraging that the method was set up in the Section Clinical Neurochemistry, NINDB. This consists of determining the growth of Lactobacillus leishmanii induced by various concentrations of cyanocobalamin standard and various amounts of extracts of serum and cerebrospinal fluid samples added to the culture medium. Growth is determined densitometrically using a Coleman Spectrophotometer. Samples of both serum and cerebrospinal fluid drawn for these assays are frozen in dry ice-acetone and kept until required. (N-8-206)

Patients for the study have been drawn from the NINDB ward population and volunteer normal controls have been recruited. Six normal controls and two patients with diseases not involving the nervous system have been used so far. Control serum and cerebrospinal fluid samples are obtained in each case. Daily parenteral Vitamin B_{12} in a dose of 1000 micrograms is then given for seven days. Twenty-four hours after the last injection, a second serum and cerebrospinal fluid sample is obtained.

(c) Major findings: The initial two cases studied (assays by Merck and Co.) suggest that a significant concentration of Vitamin B_{12} in cerebrospinal fluid occurs compared to serum over the seven day treatment period, Consistent results by the method set up at NINDB have been obtained, but the concentrations found are considerably higher than those obtained

by other laboratories for baseline levels in either fluid. Difficulties have been encountered in the extraction procedure used by previous workers particularly for serum samples and erratic growth of the test organism has occurred from time to time. Considerable effort has been expended in an attempt to standardize or control these factors, so far without much success. The majority of the samples have, therefore, not been assayed, since their validity would be liable to question. The frozen samples are being kept until experimental conditions warrant their committment for assay.

(d) Significance to Neurological Research: If preliminary results, suggesting that cerebrospinal fluid levels of Vitamin B_{12} rise significantly during a week of administration of large doses in contradistinction to little or no rise in serum, can be confirmed, this would have important bearing on dosages to be employed in Vitamin B_{12} therapy and on the mechanism of action of the Vitamin in relation to certain neurological diseases.

(e) Proposed course: When control of factors affecting the assay procedure is standardized, the remaining samples now in hand will be assayed. Comparison of these results with those for samples from patients with diseases known to be concerned with disorders of Vitamin B_{12} metabolism or utilization (pernicious anemia, diabetes, combined system disease and the like) will be made.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 99 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITIES:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW AND APPROVAL	[ ]	PROFESSIONAL AND TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

Research Division, Merck and Co., Rahway, N. J., Dr. George Boxer.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB 99 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 100 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Comparative Biochemistry of Smooth Muscle and Striated Muscle Actomyosin.
PROJECT TITLE

7. Dr. Beni Horvath
PRINCIPAL INVESTIGATOR

8. Mr. Joseph Proctor
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION

(a) Objectives: To characterize actomyosin of uterine muscle in physico-chemical terms and to study actomyosin synthesis in uterine muscle.

(b) Methodology: Myosin, actin, and other muscle proteins will be extracted from rabbit uterine muscle and skeletal muscle. The yield will be compared at various stages of development. The samples so obtained will be characterized by viscosity, electrophoretic mobility, sedimentation properties, etc. as well as by its reaction with ATP.

(c) Major Findings: For purposes of comparison between the two kinds of muscle, an extraction procedure had to be established which gives maximal yields for both types of muscle. The method of Dr. Albert Szent-Gyorgyi, originally devised for extraction of heart muscle, was also found to give excellent yields of actomyosin from small samples of skeletal muscle. This method uses potassium iodide instead of the conventional potassium chloride. It was found that a further increase in yield can be achieved by frozen sectioning of the sediment obtained by centrifugation

of the first potassium iodide homogenate of the muscle. By ultracentrifuge studies it has been shown that myosin so obtained from normal skeletal muscle (human and goat) is in the same state of aggregation as the best preparations of rabbit myosin described in the literature. Ultracentrifuge studies on other muscle fractions also suggest that the present method is more efficient in extracting actomyosin than more conventional procedures.

(d) Significance to Neurological Research; It is felt that knowledge of the formation of myosin and actin may have an important bearing on the mechanisms of the disease in muscular dystrophy. Quantitative extraction procedures are also essential to the study of muscle proteins in other neuromuscular diseases.

(e) Proposed Course; Adaptation of the above procedures to the uterine muscle of rabbits. Since ovarian hormones (estrogens and progesterone) have a marked effect on uterine development, the effects of these hormones on the time course of protein synthesis will be studied, using the quantities of actin and myosin as indicators.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 100 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57	$20,000	5,152	$25,152	.5	.5	1.
	BUDGETED POSITIONS			PATIENT DAYS		
	PROF	OTHER	TOTAL			
FY'57	.5	.5	1.			

13. BUDGET ACTIVITY:

RESEARCH ☒
REVIEW AND APPROVAL ☐
BIOLOGIC STANDARDS ☐
ADMINISTRATION ☐
PROFESSIONAL AND TECHNICAL ASSISTANCE ☐

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S):

None

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB 100 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956.

None.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 101 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Alterations of Actomyosin Tensile Strength and Characterization of Muscle Proteins in Neuromuscular Disease
PROJECT TITLE

7. Dr. Beni Horvath
PRINCIPAL INVESTIGATOR

8. Mr. Joseph Proctor, Mr. William Matthews, Dr. W.C. Curtis, Dr. G. Milton Shy
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH.).

None

10. PROJECT DESCRIPTION

(a) Objectives: To determine alterations in tensile strength of actomyosin threads prepared from muscle biopsy samples taken from patients with neuromuscular diseases. To estimate the quantity of actomyosin diseased muscles and to characterize in physicochemical terms the proteins of diseased muscles in comparison to normal muscles.

(b) Methodology: Muscle fibers are obtained from patients with various neuromuscular diseases as biopsy samples and are stored at low temperatures in glycerol. They are studied in a specially designed apparatus. For purposes of comparison with normal control samples, a procedure has been developed for expressing the tension in absolute units and as a function of the ATP concentration of the medium.

Other samples also obtained on biopsy and stored in the frozen state are used for preparation of actomyosin by the method of Dr. Albert Szent-Gyorgyi, originally devised for heart muscle and now adapted for dealing with small samples of muscle. The actomyosin so obtained is studied in the form of threads which contract on addition of ATP. The same actomyosin is also studied by physico-chemical methods.

(c) Patient Material: Muscle samples are obtained by biopsy, under nerve block anesthesia, from patients admitted to NINDB wards with various neuromuscular diseases. (N-2-012)

(d) Major Findings: On the glycerinated fibers and also on the actomyosin threads it has been found that a limited range of ATP concentrations exists where contraction occurs. There appears to be a difference between normal and myotonic muscles in the extent of this range. Because of complicating factors, statistical evaluation of the findings is required before final conclusions can be drawn, necessitating collection of more sample data.

Ultracentrifuge studies indicate that myosin prepared from dystrophic muscles is polydisperse. Under the same conditions normal muscles yield myosin which is monodisperse. By preparative manipulation it is possible to obtain three, and possibly six, myosin fractions from dystrophic muscles each characterized by a different sedimentation constant. The polydispersity of this myosin is not apparent from electrophoretic studies carried out so far.

(e) Significance to Neurological Research: Studies of the mechanical and physico-chemical characteristics of normal or diseases human muscles have not been carried out before. The possibility that the basis for a number of myopathies resides in defective contractile proteins (actomyosin) is an important area for research in muscle diseases. The results of this project so far plus those of Dr. Ruth Geiger (unpublished) with tissue culture of hyman dystrophic muscle fibres indicate that this is a real possibility. The understanding of factors in normal muscle structure and function and their derangements in neuromuscular diseases has great fundamental importance.

(f) Proposed Course: Experiments along the above lines will be amplified and extended to include other types of muscle disease. An immuno-chemical study of dystrophic myosin will be undertaken in cooperation with the Section of Clinical Neuropathology (cf. NINDB Serial No. 58 (C)). The possibility of adding to these studies by the use of specific strains of mice with a genetic form of dystrophy will be investigated. Further preparative and physico-chemical studies are proposed to obtain a more detailed description of the size and shape of myosin molecules in muscular dystrophy.

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 101 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$20,000	5,152	$25,152	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO.

Section of Clinical Neuropathology - Dr. Igor Klatzo.
Serial No. NINDB

Form No. ORP-1
October 1956
(Attachment I)

Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB 101 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 102 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Electrolyte Metabolism and Energy Metabolism in Normal and Epileptogenic Cerebral Cortex
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Maitland Baldwin, Dr. C-Ajmone-Marsan, Dr. Igor Klatzo, Mr. Edmund Peters, and Dr. Beni Horvath
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objectives: To study the in vitro metabolism of electrolytes, sodium and potassium, and of energy-producing cycles and compounds by slices of cerebral cortex from (1) human patients operated on for focal epileptogenic cortical lesions and (2) experimental animals.

(b) Methodology and Patient Material: See 1954 report (NINDB-18 (C). (N-1-201)

(c) Major Findings: No studies on this project have been carried out in Calendar 1956. In regard to electrolyte metabolism this has been because of the same problems discussed in the 1955 report - the necessity for a valid method for determining tissue electrolytes in terms of intracellular water. It appears that such a method can now be applied, using chloride as a measure of extracellular water plus determination of total water. Until mid-1956 the validity of chloride as a measure of cerebral tissue extracellular water was in doubt. In 1956 Elliott has reported studies with cortical slices in which the extracellular space measured by chloride corresponded to that for thiocyanate and sucrose. Thomas and McIlwain, also using cortical slices, have shown that normally less than 2% of total chloride is intracellular, using

incubation in chloride-free and chloride excess media. And direct determinations of neuron intracellular water by Engstrom and Glick, using x-ray absorption measurements on frozen-dried sections, have given values comparable to those of Lowry et al. obtained by chloride space measurements. It would appear, therefore, that chloride space values may be used with confidence, at least for normal samples. A conference with Dr. David Glick indicated that the x-ray absorption method would be applicable to this problem, but certain experiments must be carried out by Engstrom before the details of the method can be released. When they are available such data can be obtained to check the chloride method studies now under way.

In regard to studies on energy metabolism, these have been deferred, pending completion of the above studies and certain other projects. Considerable methodological development will be required here to adapt procedures available to the specific experimental situation. Because of time required to solve methodological problems in other projects it seems unwise to embark on these until adequate time and personnel can be assured.

(d) Significance of this project is self-evident since it brings into these studies on epileptogenic cortex two factors, electrolytes and energy supplies, which are accepted as essential to neuronal activity and function, providing much evidence for the mechanism by which seizures can occur. If these findings can be clarified and extended, many of the missing links in the chain of circumstances underlining the seizure and concerned with neuronal activity in general can be set in place. This will represent a contribution not only to the problem of seizures but to neurophysiological mechanisms in general.

(e) Proposed course: To carry out studies on incubated slices of cerebral cortex, both normal and epileptogenic, from animals and patients similar to those previously reported, but with additional determinations of total water and of total and tissue chloride concentrations. Chromatographic methods for magnesium and calcium are being developed which may be added to these studies, now set up only for sodium and potassium. If satisfactory data are obtained studies with radioactive K^{42} and Na^{24} will be carried out simultaneously, using a Nuclear gamma-ray spectrometer, to study turnover, uptake and diffusion factors in normal and epileptogenic slices.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 102 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S).

None.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB 102 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 103 (C)
SERIAL NUMBER

2. NINDB
INSTITUTE OR DIVISION

3 Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neurochemistry
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Glutamine and Glutamic Acid Metabolism in Normal and Epileptogenic Cerebral Cortex
PROJECT TITLE

7. Dr. Donald B. Tower
PRINCIPAL INVESTIGATOR

8. Dr. Maitland Baldwin, Dr. C. Ajmone-Marsan, Dr. Igor Klatzo, Dr. William C. Curtis, Mr. John Phoenix and Mr. Edmund Peters
OTHER INVESTIGATORS

9.→ IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES, OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None.

10. PROJECT DESCRIPTION

(a) Objectives: Are to study the in vitro metabolism of glutamine and glutamic acid by slices of cerebral cortex from (1) human patients operated for focal epileptogenic cortical lesions and (2) experimental animals.

(b) Methodology: Methods are essentially the same as those in the previous report on this project (1954-NINDB-15 (c)).

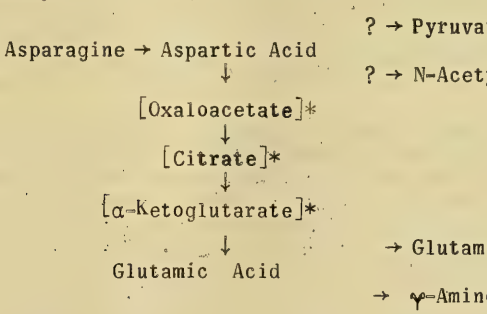
(c) Patient Material: Obtained from NINDB patients admitted to the Surgical Neurology Branch and operated on for excision of focal epileptogenic cortical foci. Since some of these excisions require removal of overlying or adjacent uninvolved cortex, a small number of non-epileptogenic samples is being accumulated. **(N-1-200)**

(d) Major Findings: This project has been prosecuted somewhat more slowly during calendar 1956 for two reasons: (1) Considerable data are already on hand obtained from established methods, while the column chromatography method with which it seemed desirable to compare the former could not be employed due to instrumentation problems, which have only now been solved; and (2) isotope studies were markedly delayed due to difficulty in obtaining additional supplies. However, from the experiments carried out,

important data have been obtained.

In the isotope studies, a satisfactory quantitative method for purification of the crude C^{14}-Asparagine sample was developed. The original sample, as received, was contaminated with 15% unreacted C^{14} - maleic acid (starting material) and 10% by-product C^{14} - aspartic acid, plus traces of at least four other C^{14} - compounds. The original sample could not, therefore, be used as such. By use of Amberlite exchange columns at appropriate pH, the maleic acid and trace contaminants were separated from the asparagine-aspartic acid fraction, and the latter was then separated into the respective asparagine and aspartic acid sub-fractions, both of which were chromatographically pure. Recoveries were at least 95% at each step. This procedure proved to be very valuable in preparation of a subsequent large batch of C^{14}-asparagine by an outside contractor, since, by making the method available to them, a pure preparation of C^{14} - asparagine was prepared and is now on hand for use.

Studies with the original purified fractions of DL-asparagine-2,3-C^{14} and of DL-aspartic acid-2,3-C^{14} added to incubated slices of normal cat cerebral cortex gave clear-cut results. Aspartic acid, under these conditions, is metabolized more readily with C^{14} activity detected in the following compounds (in order of decreasing radioactivity): glutamic acid, glutamine, gamma-amino-butyric acid,? alanine,?pyruvate and ?? N-acetyl aspartic acid. (Compounds questioned could not be verified with the limited activity of aspartic acid available.) Asparagine, under the same conditions, was less readily utilized but definite C^{14} activity was detected in the following compounds (in order of decreasing activity): aspartic acid, glutamic acid, glutamine and gamma-aminobutyric acid. No activity could be detected in alamine or N-acetyl aspartic acid fractions. These results clearly demonstrate that cerebral cortex can metabolize asparagine *in vitro* and are consistent with the following metabolic pathways.



(*-These compounds are normally present in such small concentrations that radioactivity in them could not be demonstrated by current detection methods).

The fact that the isotopically labelled 2 and 3 carbons of the 4-carbon skeleton of asparagine and aspartic acid appear in the 5-carbon skeleton of glutamic acid, and of its derived amide, glutamine, and of its decarboxylated derivative, gamma-aminobutyric acid is clear evidence of metabolism by the tissue. It is pertinent to note that the labelling of the 2 and 3 carbons of asparagine is the most suitable for

this type of study, since these two carbon atoms are not available for decarboxylation in the Krebs cycle and are not, therefore, lost to other metabolites during the study. It was not possible to extend the above experiment to human normal or epileptogenic samples because of insufficient isotopically-labelled material.

In other experiments the effects of two other compounds of the glutamic acid system were studied. Gamma-aminobutyric acid and its lactam, 2-pyrrolidinone were added during in vitro incubation of normal and epileptogenic slices of cerebral cortex from both experimental animals and human patients. No detectable effect of either could be demonstrated on metabolism of glutamine, glutamic acid or ammonia in normal slices. However, each exhibited reversal of defective glutamic acid metabolism in epileptogenic slices from patients and from cats in which seizures had been induced by either methionine sulfoximine or methyl-ethyl glutarimide (M.E.G.). The reversals in these latter cases were comparable to those obtained with equimolar concentrations of asparagine or α-ketoglutarate.

The significance of these findings is several-fold. The two compounds, γ-aminobutyrate and 2-pyrroldinone, have been found to be particularly effective in protecting M.E.G. intoxicated mice against seizures in vivo (Dr. Joseph Hawkins, Merck Institute), appearing superior to asparagine or glutamine in this test situation. Dr. K.A.C. Elliott (Montreal) and his group have identified γ-aminobutyric acid as an inhibitory factor for certain central synaptic activities, thus suggesting a function for this compound which is unique to the central nervous system. Finally the fact that the lactam of γ-aminobutyrate, 2-pyrrolidinone, is effective both in vivo and in vitro suggests therapeutic possibilities which are particularly attractive because of its ready and cheap synthesizability and its structure which makes it a neutral compound, consistent with readier intestinal absorption and blood-brain barrier penetrability. Chromatographic studies strongly suggest that cerebral tissue can split the ring to reconstitute γ-aminobutyric acid, which then enters the Krebs cycle at the succinate state and thus can support this important area of metabolism.

(e) Significance to Neurological Research: Since seizures are a major concern of NINDB as well as a major neurological problem to the population in general, knowledge of the mechanisms underlying them are essential for development of better and more rational therapy. More fundamentally, knowledge of seizure mechanisms will provide many of the factors which are concerned with neuronal function and activity in general and thus be basic to many problems of neurophysiology and neurological diseases. The defect in glutamic acid metabolism in human epileptogenic brain tissue is one of several components of a biochemical lesion of this tissue, which represents the first such lesion of a major neurological disease to be uncovered.

(f) Proposed Course: The above studies will be continued, particularly with C^{14}-labelled compounds. The C^{14}-asparagine is now on hand. C^{14}-labelled aspartic acid and glutamic acid will be purchased and negotiations are under way to obtain C^{14}-labelled glutamine, γ-amino-butyrate and 2-pyrrolidinone by synthesis. With these added to incubating cerebral slices a great deal of information about Krebs cycle and glutamic-aspartic interrelationships and metabolic activity may be obtained. In addition previous data on amino acid metabolism by cerebral tissues will be subjected to confirmation and extension by column chromatographic determination of all important cerebral amino acids (aspartic, glutamic, glycine, taurine, serine, glutamine, alanine and γ-aminboutyric) simultaneously in the same sample. The method should be ready shortly for such studies.

No. ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 103 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$21,000	5,152	$ 26,152	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW AND APPROVAL	☐	PROFESSIONAL AND TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NOH INDICATE SERIAL NO(S):

Research and Development Divisions, Merck and Co., Rahway, N.J. and Montreal, Canada

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C. Honors, Awards and Publications

15 NINDB 103 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Tower, D. B.: "The Neurochemistry of Seizures", pp. 169-197 in Korey, S.R. and Nurnberger, J.I. (Eds.): Progress in Neurobiology I Neurochemistry. New York, Hoeber, 1956.

Tower, D.B.: "Neurochemical Aspects of Pyridoxine Metabolism and Function." Am. J. Clin. Nutrition, 4: 329-345 (1956).

Tower, D.B.: "The Status of the Medical Treatment of Seizures" in Williams, D. (Ed.): Modern Trends in Neurology (2nd Ser)., London, Butterworth's, In Press.

Hawkins, J.E. and Tower, D.B. "The use of methyl-ethyl-glutarimide (Megamide) in screening anticonvulsant compounds and the anticonvulsant potency of gamma-amino butyric acid and 2-pyrrolidinone." Proc. Soc. Exp. Biol. and Med. In Press.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 104 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Neuromuscular blocking agents: Central nervous system effects.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: To directly compare the central and peripheral effects of the clinically useful neuromuscular blocking compounds.

METHODS EMPLOYED: Vascularly isolated, neurally intact head preparations of dogs and cats.

MAJOR FINDINGS: Concentrations of d-tubocurarine, succinylcholine, and decamethonium which produce prolonged apnea do not influence breathing when the peripheral neuromuscular blocking action is eliminated. This strongly suggests that the prolonged apnea which

occasionally occurs after the clinical use of these compounds, has an origin other than from a direct effect of these compounds on central structures.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: In order that clinically useful drugs may be administered other than on an empirical basis a greater understanding of this mode of action is imperative. The knowledge of how a given drug produces its observed effect thus benefits the patient and increases the safety with which it can be administered. During the time the neuromuscular blocking compounds have been in clinical use, prolonged respiratory arrest has been observed following the use of these substances during anesthesia. The prolonged apnea previously had been reported as arising from a central depressant action on the respiratory center. It is hoped that the information obtained from this project will allow the anesthesiologist to care for patients in apnea from these drugs in an improved manner.

PROPOSED COURSE OF PROJECT: Project completed.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 104 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57	$7,500	$5,152	$12,652	.5	.5	1.

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 104 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Richard L. Irwin and Jay B. Wells, "The Respiratory Activity of Certain Neuromuscular Blocking Compounds: A Direct Peripheral and Central Comparison", The Journal of Pharmacology and Experimental Therapeutics, accepted for publication.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 105 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Neuromuscular blocking compounds: Peripheral and respiratory action related to calcium, potassium, magnesium, carbon dioxide and anesthetic gases.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: To determine how changes in the concentration of physiological ions and respiratory or anesthetic gases are related to the phenomenon of neuromuscular block.

METHODS EMPLOYED: During the course of this project a method has been devised to measure the respiratory effects of neuromuscular compounds under conditions that approximate those under which this type of compound is useful. The method is not dependent on extraneous

nerve stimulation or artificial respiration. The peripheral effects have been tested by a method in which the muscle has been stimulated alternately indirectly through the nerve and directly through 2 pairs of electrodes in the muscle. This method enables the separation of direct effects upon the muscle and effects on the transmission process.

MAJOR FINDINGS: The administration of calcium is markedly antagonistic to the peripheral as well as to the respiratory effects of the neuromuscular blocking compound succinylcholine. This has been found not to be due to a direct effect of calcium on muscle fibers or to the release of adrenalin by calcium. Indirect evidence suggests that cholinesterase activation by calcium is not involved. Calcium not only antagonizes a pre-existing neuromuscular block but also decreases the depth and duration of the block when calcium is administered prior to the blocking compound. Hypercarbia reduces both the duration and depth of the neuromuscular block produced by succinylcholine in some species, in others the hypercarbia appears to have an additive effect with succinylcholine. The antagonism occurs only when acidemia has existed prior to the onset of the block and is thus the result of some physiological change that develops during hypercapnia. Anoxia, at least within the physiological limits of the cardiovascular system, has been found not to effect a neuromuscular block. Hypercarbia does not influence a neuromuscular block produced by the competitive type neuromuscular compound, gallamine.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: Myasthenia Gravis and familial periodic paralysis are neurological diseases in which both derangement of neuromuscular transmission and changes in ionic concentration in the blood may be involved. Until more knowledge on the mechanisms of a neuromuscular block and its relation to ionic concentration is available the etiology and treatment of these diseases must necessarily remain empirical. It is therefore important to examine the phenomena of neuromuscular block in greater detail than is possible in the patients.

PROPOSED COURSE OF PROJECT: The phase of the project concerned with succinylcholine, calcium and respiration is complete. The recent work on this project has shown that the effects of CO_2 and ionic changes on a neuromuscular block are complex and not readily evaluated *in vivo*. An attempt will be made to investigate this problem using isolated tissue.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 105 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT REIMBURSEMENT		TOTAL	PROF	OTHER	TOTAL
FY'57	$3,700	5,152	$ 14,052	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 105 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Richard L. Irwin and Jay B. Wells, "Effect of Calcium on the Duration of Apnea Induced by Succinylcholine", Anesthesiology, Nov.-Dec. 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 106 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Search for a circulating neuromuscular blocking substance as a causative agent in myasthenia gravis.
PROJECT TITLE

7. Peter T. Rowley, M.D.
PRINCIPAL INVESTIGATOR

8. Richard L. Irwin, Ph.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: The purpose of this project is to determine if a blood-borne substance is responsible for the clinical manifestations of myasthenia gravis.

METHODS EMPLOYED: Neuromuscular blocking action is measured in mice by sliding when placed on a 60° inclined screen. A dose of d-tubocurarine is determined which will cause a small percentage of a group of mice placed on the inclined screen to slide due to

its neuromuscular blocking action. Blood freshly drawn from fatigued unmedicated myasthenic patients is injected into the mice from half the group, and blood freshly drawn from fatigued normal persons is injected into the other half. An increase in the percentage of mice sliding in the group injected with myasthenic blood compared with the control group could be attributed to a blocking substance in that patient's blood. This method is theoretically adequate to demonstrate the presence of a quantity of a blocking compound in the patient that would produce a demonstrable block.

MAJOR FINDINGS: Too few patients have been studied thus far to permit general conclusions.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: The identification of a substance in the blood of patients with myasthenia gravis with augments the effect of a neuromuscular blocking drug in animals would facilitate the analysis of the basic biochemical defect.

PROPOSED COURSE OF PROJECT: A larger number of patients will be investigated.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 106 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$ 5,152		$ 12,652	.5	.5	1.

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.5	1.	

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 106 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 107 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Blood and tissue cholinesterases in neuromuscular blockade.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S., Peter T. Rowley, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: To determine *in vivo* what influence specific and non-specific cholinesterases have on a neuromuscular block produced by cholinesterase sensitive compounds.

METHODS: A cross circulation preparation in which the blood of a donor animal can be made to perfuse one leg of a recipient animal is being developed. After appropriate manipulation of the blood and tissue cholinesterases in the two animals, recording from both legs of the donor animal will give a direct comparison of the roles played by the two types of cholinesterase compounds.

MAJOR FINDINGS: None

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: This project will perhaps furnish additional information on the *in vivo* metabolism of clinically useful neuromuscular blocking agents as well as a greater understanding of the physiological processes related to myasthenia gravis.

PROPOSED COURSE OF PROJECT: This project is in the method developmental stage and will be continued until the above objectives have been obtained.

PUBLIC HEALTH SERVICE -- - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 107 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSIST-ANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 107 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 108 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The development of a "myasthenic" animal for testing purposes.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S., Peter T. Rowley, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: Myasthenia gravis is a neurological disorder that somewhat resembles a state of chronic neuromuscular block. The thymus gland has been considered by some investigatrs as an etiological factor. No adequate laboratory method has been described that will give information as to whether any drug will be effective in the treatment of myasthenia. The standard techniques to test for antagonism against a neuromuscular block are inadequate since the disease is not reproducible in a laboratory animal. The purpose of the present project is to develop a method for more accurate testing of drugs that may be of value in the treatment of myasthenia gravis.

METHODS EMPLOYED: The rabbit head drop method was selected as a beginning point since this method detects neuromuscular blocking activity without the complications of either electrical stimulation or anesthesia. In conjunction with Dr. Sarah Stewart of the Cancer Institute, mice with thymus tumors are being investigated as a possible "myasthenic" test animal. Unfortunately, these tumors grow slowly when transplanted and require several months for development. These mice will be tested for the presence of subliminal neuromuscular block by the inclined screen or other suitable methods.

MAJOR FINDINGS: None--laboratory animals which are given neuromuscular drugs daily for extended periods do not develop a "myasthenic like" state.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: The development of a new method for screening compounds that would be pharmacologically active in the treatment of myasthenia would perhaps aid in finding substances of clinical value. If a method can be found to produce a "myasthenic like" state in a laboratory animal it is conceivable that new information may be obtained concerning the neuromuscular processes involved in myasthenia about which little is known at present.

PROPOSED COURSE OF PROJECT: The search for a new method to test substances that may be effective in the treatment of myasthenia gravis will be continued. The possibility that the inhibition of choline acetylase *in vivo* will produce a test animal that is somewhat similar to a myasthenic patient will be investigated. The attempt to find compounds that are specific inhibitors of choline acetylase will be continued.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 108 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57				

13. BUDGET ACTIVITY:

RESEARCH	[X]	ADMINISTRATION	[ ]
REVIEW & APPROVAL	[ ]	PROFESSIONAL & TECHNICAL ASSISTANCE	[ ]
BIOLOGIC STANDARDS	[ ]		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 108 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 109 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Study of new chemical compounds with central nervous system effects.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S., William C. Curtis, Ph.D., Donald B. Tower, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: The study of chemical compounds which alter central nervous system activity is of importance for several reasons. Firstly, some compounds of this type, when adequately characterized pharmacologically, may find a useful place in therapeutics. Such substances have in the past also served as valuable research tools and have led to a greater understanding of physiological and biochemical mechanisms of disease processes. The objective of this project is to find compounds with central nervous system effects that have not been described and to investigate these compounds and others that have unusual or unexplained effects upon the central nervous system.

METHODS EMPLOYED: No method is known that will with certitude uncover pharmacologically active chemical substances. Standard pharmacological procedures of many types have been used.

MAJOR FINDINGS: One compound, thiopyrolidone, has been found to have pronounced central nervous system activity. Preliminary qualitative testing has shown that although this compound remarkably lowers spontaneous activity in at least 3 species of laboratory animals. Preliminary testing also indicates an analgesic activity without hypnosis or anesthesia. Although motor activity is markedly reduced, no anticonvulsant activity could be detected. The acute toxicity is low, the LD_{50} in mice and rats is greater than 500 mg/Kg. Thiopyrolidone does not appreciably affect blood pressure of the rat or dog in large doses administered rapidly. These preliminary tests suggest that this compound may be an ataraxic drug of some interest.

SIGNIFICANCE TO PROGRAM OF INSTITUTE: See objectives. This project is perhaps of more general interest than specifically related to an institute program.

PROPOSED COURSE OF PROJECT: To further characterize pharmacologically thiopyrolidone and related compounds. To continue to find and investigate other compounds which effects upon the central nervous system.

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 109 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57			0			0

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 109 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 110 (C)
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LABORATORY, BRANCH, OR DEPARTMENT

4. Clinical Neuropharmacology
SECTION OR SERVICE

5.
LOCATION (IF OTHER THAN BETHESDA)

6. The action of drugs on directly stimulated innervated and denervated muscle.
PROJECT TITLE

7. Richard L. Irwin, Ph.D.
PRINCIPAL INVESTIGATOR

8. Jay B. Wells, M.S., Peter T. Rowley, M.D.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

OBJECTIVES: An understanding of the site and mechanism of drug action often provides insight into the pathological physiology or the biochemical basis of disease. Furthermore, a knowledge of the fundamental mechanisms by which a drug changes the physiological function of a tissue invariably leads to a more effective therapeutic application. With these two general concepts in mind, a research project was established to investigate the function of directly stimulated muscle in relation to clinically useful drugs which affect muscle contraction.

METHODS: In the experiments with innervated muscle, a method has been developed which has enabled us to separate the effect of the drug at the neuromuscular junction from any effect it may have at a post junctional site. The effect of nerve stimulation is eliminated by fatigue through the nerve or the administration of a neuromuscular blocking agent. The response of denervated muscle has been compared directly to that of innervated by the use of pairs of muscle in the same animal. The effects of sudden changes in drug concentration is to be investigated by means of a cross circulation preparation in which the blood of two animals can be made to alternately perfuse an isolated leg.

MAJOR FINDINGS: In innervated muscle, neuromuscular compounds which are known to compete with acetylcholine for receptor sites do not influence contraction following the direct stimulation of muscle. On the contrary, neuromuscular blocking agents which prevent transmission by an initial depolarization of the motor end plate reduce the contraction of directly stimulated muscle by an average of 50 per cent. The decrease in contraction cannot be overcome by an increase in stimulus voltage. A several fold increase in dose does not reduce the contraction by more than 50 per cent. Muscles which have been denervated for seven days are more sensitive than innervated to this effect of the depolarizing drugs. Denervated muscles respond with a more pronounced and rapid reduction of contraction height. Recovery from the drug effect is slower. The prior administration of a competitive type neuromuscular blocking compound completely prevents the effect of the depolarizing compounds in innervated but not in denervated muscle. Indirect evidence indicates that the action of the depolarizing compounds in innervated muscle does not arise from the spreading of depolarization from the end plate to the rest of the muscle fiber--but that the effects are either directly on the muscle membrane away from the end plate or on contractile process or processes which initiate contraction.

SIGNIFICANCE TO THE PROGRAM OF THE INSTITUTE: This project is a fundamental study related to the muscle disease program of the clinical research division. It is hoped that this investigation will lead to a greater knowledge in pathological physiology of muscle disease.

PROPOSED COURSE OF PROJECT: The portion of this project concerning directly stimulated innervated muscle is essentially complete and a manuscript for publication is in preparation. The study with denervated muscle is being continued. The mechanism of the reduction in contractile force will be investigated. A preliminary report on this work has been presented to the American Society of Pharmacology and Experimental Therapeutics.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB 110 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,500	5,152	12,652	.5	.5	1.

	BUDGETED POSITIONS		
	PROF	OTHER	TOTAL
FY'57	.5	.5	1.

PATIENT DAYS

13. BUDGET ACTIVITY:

RESEARCH [X]
REVIEW & APPROVAL [ ]
BIOLOGIC STANDARDS [ ]
ADMINISTRATION [ ]
PROFESSIONAL & TECHNICAL ASSISTANCE [ ]

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 110 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB 111(C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LAB., BRANCH, OR DEPT.

4. Biophysical Applications
SECTION OR SERVICE

5. -
LOCATION (IF OTHER THAN BETHESDA)

6. Investigation, Localization Cerebral Neoplasia by Isotopic Detection
PROJECT TITLE

7. G. Milton Shy and Robert Bradley
PRINCIPAL INVESTIGATORS

8. _____
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN N.I.H.). -

10. PROJECT DESCRIPTION

Objectives: An attempt to localize brain tumors by utilization of isotopic detection. Objectives of this project are a study of primary and secondary cerebral neoplasias; an attempt at preoperative localization and to demonstrate the extent of such tumors as well as to obtain further indications of their metabolism.

Methods Employed: The methodology of this procedure is somewhat complex. To date the following methods have been utilized: The study was started with Zinc-65. This was based upon Zinc uptake in mouse melanomas. In addition, brain tumor activation analysis of cerebral neoplasia was carried on at Oak Ridge National Laboratory. Zinc-65, however, has a half-life of 260 days and an energy of Mev 1.1. This is not, therefore, an ideal isotope and utilization was limited to 200 microcuries or less. Negotiations

Methods Employed (Cont'd.): with Abbott Laboratories at Oak Ridge National Laboratories has yielded an isotope with a purity of approximately 80 percent Zinc-69, half-life 14 hours, Mev .44. The other 20 percent of the received isotope, however, is still Zinc-65. This and RISA are the two isotopes used to date in this study. This is administered by intravenous technique and the patient is placed in such a position to enable continual scanning of lateral, AP, and PA projections of the skull. To more clearly delineate the edges of the neoplasia, a collimator devised by Frances and Bell of the Oak Ridge Laboratories has been utilized. This collimator has not been satisfactory, however, since it was designed for a point source and sensitivity has dropped to the point that tumors may readily be missed. More recently, an open hole collimator has been used to detect the tumor and then the Frances-Bell collimator used to mark the edges. This, in turn, goes through a pulse-height analyzer. From the pulse-height analyzer two leads are taken; one goes to a Brown recorder, in which sensitivity may be so arranged that the background may be removed and total magnification recorded so that changes of activity which might be missed on scaler circuits could be seen here. In addition, from the pulse-height analyzer, an additional lead goes to a scaler which, in turn, activates a mechanical tapping device. On the back of the Brown recorder, in turn, leads are lead to a photo recording system by way of neon lights for infra-red photography. One of the difficulties has been the general increase in activity of neck muscles where approached. A condenser coupled amplifier has, therefore, been constructed which will give changes under approximately 15 seconds and reject changes over this duration. This is an attempt, therefore, to mask out the increasing gradual activity as the neck muscles are approached, one sweep taking approximately 2 minutes.

Patient Material: Patient material came from NINDB patients admitted for tumor suspect or from the National Cancer Institute with metastatic tumor to brain. Approximately 7 such cases have been done to date. (N-12-900)

Major Findings: Superficial neoplasia offers no difficulty to localization. The major difficulties are in deep neoplasias. Specific neoplasias such as thyroid tumors again offer no difficulty and may be readily picked up by the use of RISA. Their edges may be delineated by use of the Bell (collimator). Metastatic tumors and deep lying tumors other than metasteses have been unsatisfactory to date with the exception of gliomas in which 80 percent success has been reported, even in gliomas of the posterior fossa. The problems facing this project are as follows: First of all, the collimator must be re-designed, and we are now doing so, in which a sensitive volume is scanned instead of a point. Certainly the interstices of the collimator must be of significant density to stop the penetration of hard gamma radiation (i.e. above .75). Such a collimator is being constructed of gold at the present time. This gold may, at the end of the project, be recast, sent back to the

Major Findings (Cont'd.): mint, and the funds returned. Third, attempts are being made in collaboration with the Oak Ridge National Laboratory to obtain pure Zinc-68 which will give a pure Zinc-69. At the present time, Zinc-65 will release x-radiation within the collimator within the range of .44 Mev and hence obscure the localization from Zinc-69. Attempts will be made to find isotopes other than Zinc which may be useful in this regard.

Proposed Course of Project: To construct a sensitive-volume collimator. 2. To obliterate surface activity by means of the process listed above. 3. If successful, the research part of this project will terminate; the apparatus will be turned over to the Section of Neurological Surgery for operation.

Significance to Neurological Research: Present localizing techniques by way of arteriography and pneumography for intracranial neoplasia are unsatisfactory in that they do not give a true picture of the total extent of the neoplasia and are traumatic to the patient. If other methods of intracranial localization with less risk to the patient can be devised, this will be of major significance.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 111 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$35,000	5,152	$40,152	2	2	4

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	

FY'57

2.	2.	4

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES

OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 111(C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB 112(C)
SERIAL NUMBER

2. Neurological Diseases & Blindness
INSTITUTE OR DIVISION

3. Medical Neurology
LAB., BRANCH, OR DEPARTMENT

4. Biophysical Applications
SECTION OR SERVICE

5. -
LOCATION (IF OTHER THAN BETHESDA)

6. Protein Studies in Neuromuscular Diseases and Hereditary Ataxia
PROJECT TITLE

7. G. Milton Shy
PRINCIPAL INVESTIGATOR

8. Robert Bradley
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH (BY SERIAL NO.(S) IF WITHIN N.I.H.). -

10. PROJECT DESCRIPTION (N-10-007)

Objectives: This project will now combine Project NINDB-2 and NINDB-5 of the 1955 report. Both projects will now be undertaken by the Applied Biophysics Section of the Clinical Investigative Unit. The objective is to determine the origin of the gamma globulin in spinal fluid in certain degenerative disorders, notably spinal cerebellar ataxia, and to account for the high radioiodinated albumin in dystrophic muscle and the appearance of free iodine in excessive amounts in the urine of dystrophic muscle.

Methods Employed: It now becomes of importance to find whether such gamma globulin is a result of degenerative brain products, or whether this represents abnormality in the formation of gamma globulin and beta globulin which is merely reflected in the spinal fluid. Fortunately, the majority of globulins containing

Methods Employed (Cont'd.): metalic ions lie within the beta globulin range and are increased also in these diseases. They are apparently, however, incorporated in beta globulin fractions such as ceruloplasmin only in the formation of the globulin. Up unto this point they are carried by the albumin fractions. Thus, at 6 hours the majority of radioactive tag Copper-64 lies in the albumin fraction. At 48 hours, it lies in the beta globulin fraction. If, however, the beta globulin is not formed, then the radioactive tag stays in the albumin fraction. If the beta globulin found in the spinal fluid in the degenerative disorders is, therefore, a product of brain destruction, it may carry comparatively more protein than tags than does the outside due to the blood brain barrier. If, however, this merely represents the diffusion after normal globulin exchange has occurred, then the spinal fluid should, like the urine, reflect the blood proteins. This, then, could be utilized as a screen method. If positive, it would be of value; if negative, no more information would be at hand. Horvath, Berg, Shy, and Cummings pointed out originally there is a high activity of radioactive iodine in muscular dystrophy from dystrophic biopsies. There is, in addition, a high amount of iodine in the urine. There is also an increase, found by Dr. Curtis, of oxyproteic acids in the urine. It becomes important to find if such protein was broken down before entering muscles or while still in the blood stream. Radioactive iodine disappearance curves combined with separation of oxyproteic acids, and subsequent studies of the activity by Dr. Curtis (see project #95), will be of value in further ellucidating this problem.

Major Findings: Electrophoresis has indicated that in a spinal cerebellar ataxia a significant amount of gamma globulin is found within the spinal fluid ranging to 46 percent of the total protein of the spinal fluid. This has been found by Doctors Jaffe, Wells, Korengold, and Curtis in the past two years.

Proposed Course of Project: Proposed course of project as above.

Significance to Neurological Research: This is of importance in the basic understanding of protein metabolism in degenerative diseases and in the formation of muscular dystrophy.

ORP-1 Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data 11. NINDB 112 (C)
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$35,000	5,152	$40,152	2	2	4

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2	2	4	

13. BUDGET ACTIVITY:

RESEARCH	☒	ADMINISTRATION	☐
REVIEW & APPROVAL	☐	PROFESSIONAL & TECHNICAL ASSISTANCE	☐
BIOLOGIC STANDARDS	☐		

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S)

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB 112 (C)
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None since previously noted.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

NONE

Annual Report of the Basic Research Program, NIMH-NINDB

January 1 to December 31, 1956

The past year has seen an increasing appreciation of the importance of basic research to mental and neurological disease and a revival of interest in biological etiologies and techniques of therapy in psychiatric illness. In testimony before the Congress and in the Congressional Appropriation Committees' reports, there was explicit indication of a recognition of the value of fundamental research in progress toward an ultimate solution of numerous, pressing medical problems. The beneficial symptomatic effects of the so-called "tranquilizing" drugs has created considerable popular and scientific interest in the newly rediscovered science of psychopharmacology and has swung the pendulum of psychiatric theory toward those hypotheses which emphasize the biological basis of mental illness. From its inception in 1951, the Basic Research Program has stressed the importance of fundamental and biological research to the clinical problems of both Institutes. Studies relating to the biochemical and physiological mechanism of action of psychopharmacologic agents have antedated the widespread interest in this field, and, in the current year, research in this discipline has progressed so that practically every laboratory has concerned itself with one or another aspect of the problem.

There is a danger in the overemphasis of the purely biological aspects of illness, especially psychiatric illness. One explanation for the wide swings in psychiatric theory between the organic and the psychosocial sciences has been the inescapable fact that both of these areas are relevant to mental illness, yet neither alone can emcompass a complete explanation. There is emerging a modern concept that these illnesses represent an interaction between experiential and environmental factors upon a constitutional, biological substrate, and a research program which emphasizes one of these approaches to the detriment of the other is not likely fully to exploit the potentialities of science in the understanding of disease. The Basic Research Program represents a conscious effort to provide a broad base of fundamental research in all of the biological and behavioral sciences which may contribute to an understanding of neuropsychiatric illness. One of the hoped for consequences of a propinquity of outstanding representatives of these various disciplines was an interaction among them and the emergence of research undertakings of a multidisciplinary nature, for it is the areas between disciplines which tend to be neglected as the individual scientist pursues his own research interests with

theory, background, and techniques with which he is most familiar and in which he is most competent.

Examples of many of these cross-disciplinary undertakings are found in the succeeding summary. There are projects in which biochemists and biophysicists have collaborated on studies of the biochemical processes involved in generation of the nerve impulse. There are numerous multidisciplinary projects on the relationship between neuroanatomical and neurophysiological changes and behavior. There are many projects which interrelate pharmacology with biochemistry and physiology on one hand, the behavioral and clinical sciences on the other. The program of aging has been attacked from a multidisciplinary point of view ranging all the way from anatomical studies through biochemistry, physiology, psychology, and sociology to clinical psychiatry and neurology. One important attribute which these multidisciplinary projects have is that they emerged spontaneously from the scientists themselves rather than being directed from above. In this way, they retain the originality and initiative which is most essential for creative, scientific effort.

The most notable addition to the Basic Research Program, which took place in November of 1956, was the appointment of Dr. Robert B. Livingston as Director of Basic Research. Dr. Livingston comes to this post with a distinguished background in neurophysiological research, in teaching, and with a demonstrated and mature appreciation of the implications of fundamental research to mental and neurological problems. He succeeds Dr. Seymour S. Kety who, after five years in that post, will return to full-time research as Chief of the Laboratory of Clinical Science. It is gratifying also to report the appointment of Dr. Sanford Palay, who has made important contributions to the knowledge of the ultrastructure of the nervous system, as Chief of the Section on Neurocytology in the Laboratory of Neuroanatomical Sciences. The appointment of Dr. Horace W. Magoun as a Visiting Scientist during his sabbatical leave from the University of California has provided a stimulating opportunity to the staff to associate intellectually with a distinguished neurophysiologist. This program suffered a significant loss when Michael Davis, Chief of the Section on Technical Development, resigned to accept a research position with the General Electric Company. His comprehension of biological problems and engineering skills played an important role in the research progress of the entire program.

The remainder of this report consists of the summaries of the activities and progress of the various laboratories and a detailed description of the individual research projects.

Seymour S. Kety, M.D.

LABORATORY OF NEUROANATOMICAL SCIENCES
William F. Windle, Chief

All current budget positions of the Laboratory of Neuroanatomical Sciences have been filled and its organizational pattern is complete. There are 12 scientists occupying permanent positions, 3 visiting scientists on four-month to one-year tenure and 2 consultants. It is anticipated that by the end of this calendar year the laboratory should be able to move into the east wing of Building 9.

Neurocytology. The scientific personnel of this section are Dr. R. Wayne Albers, Dr. Milton W. Brightman, Dr. Samuel McGee-Russell (visiting scientist from the University of London) and Dr. Sanford L. Palay, Chief. With the exception of certain projects of Drs. Albers and Brightman, the activities of this section have been confined to planning and to "library research", but facilities for experiments will soon be provided in Building 9.

Drs. Palay, McGee-Russell and Brightman are planning to study the ultrastructure of the nervous tissue, particularly the synapse and neuroglia, with special attention to correlation between structure and function. The principal instrument to be employed will be the electron microscope which has already revealed the ultrastructure of the synapse in some detail. The meaning of the ultrastructure in terms of function awaits discovery. It is important to have functional correlates for the ultrastructure revealed by electron microscopy for an understanding of the mechanisms of impulse transmission. Other studies are planned to shed light on the structure and function of the neuroglia.

These and studies in neuroglia in other sections of this laboratory were stimulated by a conference on "The Biology of Neuroglia" which was held at Stone House last March. The transcription of the papers and discussions of this conference are at present being edited and soon will be published as a monograph.

Dr. R. Wayne Albers has continued his quantitative histochemical studies of the nervous system, modifying methods of biochemistry for microgram and submicrogram samples of tissue. He and others of the section have developed a new and simplified technique for measurement of cholinesterases and are about to publish this. The microbiochemical techniques have been discussed by Dr. Albers in one chapter of a monograph on "New Research Techniques of Neuroanatomy," in press.

Additional light has been shed on the neuroglia through a comparative study of normal and atrophic magnocellular laminae of the lateral geniculate body. After bringing about atrophic loss of nervous elements in this, it was possible to study tissue-lacking neurons but rich in neuroglia cells. The enzymatic contribution of the neuroglia was found to be a significant fraction of the total for this part of the brain.

In other experiments, it was found that a protein fraction extracted from the posterior pituitary gland of the rat appears to be related to, if not identical with, the neurosecretory product of that part of the gland. Dr. Milton W. Brightman participated in the latter experiment.

Experimental Neuropathology. The scientific personnel of this section are Dr. Helen J. Ramsey and Dr. Jan Cammermeyer, Chief.

They have continued to accumulate information about histological and physical qualities of the mammalian spinal cord which are significant in maintaining proper circulation of blood and tension of the tissue. The studies have demonstrated labile physical qualities inherent in the spinal cord which probably play an important role in the maintenance of normal cord function and which mitigate against damage by concussion, ischemia, demyelinating influences, etc. Another project studied by Dr. Cammermeyer is interstitial hypertrophic polyneuropathy (Refsum's syndrome); this has been completed and an article is in press.

Dr. Ramsey is conducting studies on the distribution of extradural fat in mammals to determine factors permitting movement of the vertebrate column and of the spinal cord within it in relation to the spinal blood supply. No systematic study of the distribution of extradural fat has been published. It is necessary to carry out this study to understand factors which contribute to maintenance of pressure on the spinal cord under normal conditions and in certain pathological states. Another investigation of a gross morphological nature, having to do with the blood supply of the spinal cord, is being completed by Dr. Brightman.

Functional Neuroanatomy. The scientific staff of this section consists of Dr. Leo C. Massopust and Dr. Grant L. Rasmussen, Chief.

Dr. Rasmussen has continued to perfect his new technique for selective silver impregnation of synaptic endings. He has succeeded in improving the reliability of this method and is carrying out a number of studies with it. The technique will be published for the first time as a chapter in a monograph entitled "New Research Techniques of Neuroanatomy". This

monograph represents transactions of a small conference on the subject which was held in this laboratory last February and sponsored by the National Multiple Sclerosis Society.

With this new technique for staining synapses, it is possible to observe the exact termination of intermedullary neurons more completely than previously. An effort is being made to trace the course and termination of the various fiber constituents of medial longitudinal fasciculus with this technique and with the Nauta method for degenerating axis cylinders. Considerable time will be required to carry out the large volume of histological work which this entails before final conclusions can be reached. Since exact knowledge of neuronal connections in most parts of the central nervous system is completely lacking, any concerted effort to obtain this knowledge is eminently worthwhile.

Dr. Rasmussen has continued his studies of auditory afferent and efferent systems including the autonomic innervation of the inner ear. An article entitled "A numerical and fiber caliber analysis of the cochlear vestibular nerve and its branches of the macaque, the cat and guinea pig" is in press.

Dr. Massopust and Dr. Rasmussen have begun an anatomical and physiological study of the ascending and descending visceral efferent connections of brain and spinal cord, accurately placing lesions in visceral nuclei and tracing fiber tracts from them in cats. The pathways for temperature regulation are under investigation.

Development and Regeneration. The scientific personnel of this section are Dr. Clark J. Bailey, Dr. Lloyd Guth, Dr. Irene Miali, Dr. Richard L. Sidman, Dr. William F. Windle, Chief, and visiting scientists, Dr. Paul Glees of Oxford, England, and Dr. Marisa I. R. Ramirez de Arellano of San Juan, Puerto Rico. There are two consultants, Dr. Harry H. Wilcox of the University of Tennessee, and Dr. José G. Frontera of the University of Puerto Rico.

One area of research may be characterized as the study of normal structural and functional development of the nervous system. Knowledge of intrinsic development of fibers in the human brain is scanty and there has been no systematic study reported. Such a study is underway, utilizing silver stained human embryos of the fourth to eighth week of gestation.

Another approach to the problem of development in the nervous system is by tissue culture; Dr. Richard L. Sidman is organizing a tissue culture unit. Fragments of mammalian organs can differentiate and maintain intact normal structure in vitro, thus permitting studies of direct effect of chemicals, hormones, electrical stimuli, etc.

Yet another aspect of the subject has to do with brain structure from birth to extreme old age. Studies are in progress at the University of Tennessee (under contract with this laboratory) by Dr. Wilcox, who has collected a series of brains of guinea pigs from 78 days to 2,765 days of age. The thorough study by Dr. Wilcox is the first one in any species in which factors of fixation and histological preparation has been accurately controlled.

Regeneration in the central nervous system continued to be investigated, although no major findings can be added to the last report. An article on "Regeneration in the Cord of Spinal Monkeys" was published. The conclusion reached from this study was that some regeneration of intraspinal neurons occurred in spinal monkeys under therapy with the drug, Piromen. Even under the most favorable conditions, however, regeneration was slight in contrast to that in cats and with that of extramedullary spinal nerve root fibers. The intraspinal neurons that were regenerating soon were choked off by a dense collagenous scar and no functional restitution ensued. The transactions of the conference on "Regeneration in the Central Nervous System", held two years ago, were finally published as a monograph by the same title by Charles C. Thomas, Springfield, Illinois. An article on the subject is in press in Physiological Reviews.

Certain factors involving regeneration in the peripheral nervous system continue to be studied by Dr. Lloyd Guth in an effort to determine the extent of which functional and morphological specificities of mammalian nerves are fixed and the extent to which they may be altered. Heterogeneous nerve regeneration following vago-sympathetic anastomosis led to return of normal ear temperature function; this was dependent upon the integrity of a "foreign" vagus nerve rather than being a passive phenomenon. In other experiments, Dr. Guth transected the glossopharengeal nerve, which led to the disappearance of all taste buds on the circumvallate papillae and to replacement by stratified squamous epithelium. The epithelium of the papillae atrophied, even in regions that were completely devoid of taste buds. Reinnervation of papillae by a glossopharengeal or a vagus nerve resulted in redifferentiation of the taste buds. The heterogeneous innervation by a hypoglossal nerve

appears to result only in a temporary reappearance of the taste buds. The trophic relationships between nerve and epithelium and nerve and taste buds are among the few well documented trophic nerve effects in the adult mammal. Dr. Guth has thoroughly reviewed the subject of regeneration in the peripheral nervous system in an article in Physiological Reviews.

Experiments with reserpine and other drugs in the cat, monkey and chimpanzee have been continued by Drs. Glees, Windle and others, with the object of studying hypokinesia, tremor, rigidity and related phenomena. Reserpine in a single dose of 2.5 mg/kg resulted in the appearance of a series of phenomena in monkeys somewhat like those in human patients with parkinsonism. These were transient in monkeys, lasting less than 48 to 72 hours. In cats, comparable single doses or multiple daily doses of reserpine led to more prolonged effects.

Monkeys have been kept on low daily doses of reserpine, 0.2 to 0.6 mg/kg., for as long as 13 months. They have attained states of marked and violent resting tremor which occur almost continuously, exacerbating cyclically three to five hours after each daily dose of the drug. Histological examinations of the brain have not been completed.

In chimpanzees daily doses of reserpine, 0.2 to 0.4 mg/kg, for two to four weeks enlisted bizarre behavioral reactions in which tremor, rigidity, lethargy, akinesia and other phenomena have been observed. Curious spasmodic muscle twitches and muscle contractures also appeared.

Preliminary studies have been carried out with monkeys rendered chronically tremorous with reserpine (0.2 to 0.6 mg/kg). Anesthetization of one globus pallidus through a small catheter, implanted in the brain with the Horsley-Clarke instrument, led to diminution or abolition of the tremor contralaterally. Production of an alcohol lesion in one globus pallidus and ansa lenticularis led to more enduring reduction in the tremor and rigidity.

Effects of anoxia at birth on brain structure and function in the guinea pig have been investigated during the past year. Late fetal and newborn guinea pigs were asphyxiated, resuscitated and observed for changes in behavior and for impairment of ability to learn a simple maze problem. A close correlation between the degree of asphyxia and severity of neuromuscular damage after resuscitation was established. A feasible technique for the application of scalp electrodes in the guinea pig was developed and observations were made on the effects of asphyxia and resuscitation of the electroencephalogram. Technically acceptable EEG recordings, without

the use of anesthesia, were obtained in 53 asphyxiated and controlled young guinea pigs. The data are being analyzed by Dr. Marisa I. R. Ramirez de Arellano.

Two review articles on the subject of the interrelation of asphyxia neonatorum, cerebral palsy and mental retardation are in press. A conference on "Asphyxia Neonatorum, Brain Damage and Impairment of Learning" was held in San Juan at the end of August. The transcription of this conference is being edited for publication.

LABORATORY OF BIOPHYSICS
Kenneth S. Cole, Chief

Somewhat satisfactory progress has been made in the study of the ion movements across the nerve membrane which are fundamental to impulse initiation and propagation.

The ionic current flow across the membrane of the squid giant axon was first directly measured in 1947, but continuing development of experimental procedures seems now to have resulted in data much more satisfactory than any obtained earlier. The reasonably stable surviving axon is capable of considerably more powerful activity than found previously. Although the analysis of the currents into sodium and potassium components is just beginning, it appears that the conventional modifiers of axon activity so far investigated may act on both the sodium and potassium permeabilities, but are more apt to exert their major effect on the former.

Although the squid axon continues to be the only preparation for which this ionic information can be obtained, a considerably smaller lobster giant axon has been found to be interesting and reliable and possibly a sometime companion to the squid axon. However, the myelin of the medullated frog nerve fiber may provide the necessary electrical constraints and an investigation of the ionic permeabilities of the nodal membrane has been initiated. A series of synthetic anticholinesterases have been found to block conduction in frog nerves, in inverse proportion to their positive charge.

Preparations have been made to carry out more, but less exact, computations of the physiological implications of empirical ionic conductance equations on an analog computer and to pose the digital computers with the more difficult and more critical problems. The direct calculation of a uniformly propagating impulse was not complete or adequate at the limit of the Standards Eastern Automatic Computer.

Some analytical investigations of the nature of threshold phenomena, of the iron wire analog of nerve, and of ion movements in a fixed charge membrane made satisfactory but not noteworthy progress.

LABORATORY OF NEUROPHYSIOLOGY
Wade H. Marshall, Chief

Special Senses. This section continues its high rate of productivity. Dr. Tasaki has extended his observation on the source of the steady potential in the cochlea. He is also continuing brilliant experiments on the fundamental nature of the nerve impulse and has advanced a theory that the all-or-none property of the nerve fiber is the result of transition of the membrane between two stable states. The link between the chemical and physical processes is being sought.

Drs. Tasaki and Hagiwara have conducted a highly original investigation on a synapse in the squid stellate ganglion. This synapse measures about 0.1 x 1 mm. Using two to three microelectrodes, they have ingeniously recorded from the individual cells. One of their most important results is the most definite proof yet obtained that the synaptic transmission was not mediated by the action current, supporting the chemical theory.

Dr. Spyropoulos is continuing an interesting investigation on the modes of action of nerve fibers as affected by prolonged tetanus and high pressure. Both manipulations result in a marked prolongation of the action potential to a form resembling that of the unique action potential configuration of the cardiac muscle cell. The prolonged nerve spike and the cardiac muscle cell spike are similarly affected by several chemical agents. These and other items suggest that he may be close to an important discovery of the essential factors involved.

Spinal Cord. This section is continuing the intensive investigation of the spinal neurones using microelectrode techniques. Very surprising evidence has been obtained that the neurone may discharge an impulse through the axon without the cell body membrane discharging. This does not simplify the mechanism but provides another variable which can help account for the known capacities of the nervous system. Drs. Frank and Fuortes have also secured more conclusive evidence that the cell membrane does fire only when it is depolarized to a certain critical value and that the time course of the synaptic potential indicates a chemical mediator. They are experimenting with microinjection techniques in an attempt directly to make observations on chemical mediators.

General Neurophysiology. Dr. W. H. Freygang is conducting an investigation of the synaptic transfer process in the lateral geniculate nucleus. Using very small electrodes, he isolates reactions which must be the result of activity in the small terminations of the optic tract fibers and the dendrites of the radiation cells. These reactions are much longer in duration than the impulses in the optic tract which initiate the reactions. The reactions also show the property of summation. In effect, we thus have a mechanism to approximately resynthesize the original environmental stimulus. The input at the eye is converted into a pattern of all-or-none impulses in the optic tract for purposes of transmission. At the junction in the lateral geniculate these brief impulses are prolonged in the fine terminations of the optic nerve which structures do not operate in all-or-none fashion as the tract fibers do. This and the summation activity results in a direction toward resynthesis of the original pattern before it was coded for transmission in the optic nerve. This is an oversimplified statement. Something very definite of this sort occurs, however, and Dr. Freygang has data sufficiently quantitative to begin serious calculations to determine just how the pattern is reintegrated at the geniculate synapses after having been coded for digital transmission in the optic nerve.

It has been determined that an anesthetic (nembutal) in very low doses prolongs recovery time and this in turn alters patterns of activity and that the same effect occurs after blunt instrument section of brain stem, showing that this anesthetic effect is not dependent on integrity of brain stem. It has also been shown that similar sections of the brain stem do not cause a different excitability cycle for the lateral geniculate from that seen in the conscious implanted electrode preparation.

Work is now proceeding with the consultation of Dr. Magoun. Electrodes have been placed in the recruiting and augmenting systems of several cats. Other preparations will be made with electrodes in various parts of the brain stem activating system described by Magoun, the transcollosal system, and Bishop's suprasylvian striate (axodendritic system). These experiments are designed to obtain sensitive measurements on interaction of these systems as estimated by changes of patterns of activity. Such an approach is also invaluable for drug studies and for observing behavior phenomena concurrently with the evoked and spontaneous electrical patterns.

Dr. Evarts has already made some surprising observations with these preparations. For instance, it has been considered a fact that the recruiting response could be clearly obtained

only in an anesthetized preparation. This appears to be false, the conscious cats with no drugs and little restraint show very good recruiting reactions.

Likewise, it has been claimed that LSD blocks the recruiting reaction in very low doses. This is also not confirmed in these preparations.

Work is being continued using the oxygen electrode techniques. It has been shown that oxygen tension and consumption in cortex are reciprocally related in the spreading depression process, and that the oxygen changes are secondary to the depression process.

Cortical Integration. This section is proceeding with their excellent technique for conducting experiments on restrained but unanesthetized monkeys. The brain is being explored to produce a general map of specific regions producing various reactions such as movement, emotional or emotionally associated reactions such as rage, fright, and pleasure. Old's observations on the rat (animal-start-the-stimulus) have been confirmed and extended in considerable detail.

Dr. Lilly's experiments are very important for both basic physiology and psychology and have very clear implications for theoretical psychiatry. For instance, the animal-start-the-stimulus results seem to fall into two possible classifications. One appears to involve a pleasurable reaction. The other class does not. The inference of this for analysis of mechanisms of obsessive-compulsive behavior is obvious.

Development of the bavatron techniques is proceeding toward automatic contour mapping from a 256 electrode recording array.

LABORATORY OF NEUROCHEMISTRY
Seymour S. Kety, Acting Chief

With the increasing realization on the part of biochemists that the onetime useful concept of the "unity of biochemistry" was based upon the ubiquity only of the most primitive and common of cellular functions, there has developed in recent years considerable interest in chemical differentiation and those highly specialized chemical systems which underlie the separate functions of individual tissues and organs. Neurochemistry, which early recognized the biochemical specialization in the case of the nervous system, is now receiving greater recognition as a fundamental science and

a substantial growth in its importance is to be expected. Completion of the final stage of construction in the laboratory areas of the Clinical Center should make available the space for completing the organization of the Laboratory of Neurochemistry with the appointment of the laboratory chief and his immediate staff. At the present time, this laboratory consists of three independent sections.

Lipid Chemistry. The principal efforts of this section, under Roscoe Brady, are devoted to investigations of the metabolism of complex cerebral lipids. That this problem is extremely difficult is affirmed by the scarcity of contributions made in this field and the paucity of investigators sufficiently courageous to invest in the long, relatively unspectacular, periods of effort which are required. This section, during the past year, has made significant progress in this field.

The biosynthesis of complex lipids of brain and nerve tissue has been investigated from several fundamental points. Since cerebrosides are among the more prevalent lipids, studies were begun of the formation of these compounds by examining the incorporation of galactose into the cerebroside molecule (NINDB-NC5). After in vivo aspects of the problem had been completed, the biosynthesis of cerebrosides in vitro was investigated, and it has been successfully demonstrated for the first time that the incorporation of galactose into cerebrosides is catalyzed by enzymes present in the microsomal fraction of cell-free preparations of brain tissue. This finding represents a very significant step forward because it is now possible to study the intimate nature of this process and the source of energy and co-factors which are required for this reaction.

It is apparent that a knowledge of nucleotide formation and turnover in brain is important for a better understanding of the factors which regulate complex lipid formation. Accordingly, this section is investigating the rate of formation of nucleotides in the growing rat brain and quantitatively evaluating certain enzymes which are responsible for the formation and destruction of particular nucleotides (NINDB-NC6).

Another portion of the cerebroside molecule is a long chain fatty acid joined to sphingosine. This laboratory has completed two series of fundamental investigations dealing with the synthesis and oxidation of fatty acids. The first of these studies (NINDB-NC12) dealt with important factors which regulate lipogenesis. It was found that the addition of a constant supply of a certain co-factor, reduced triphosphopyridine nucleotide, increased fatty acid synthesis from

10 to 100 fold over control values. Furthermore, the addition of free coenzyme A inhibits fatty acid synthesis drastically, whereas the same quantity augments fatty acid oxidation. Furthermore, distinct evidence for a separate pathway for fatty acid synthesis and oxidation has been demonstrated. The knowledge of these factors which have such an important influence on fatty acid metabolism may be of fundamental value in conditions in which drastic abnormalities of fatty acid metabolism occur such as arteriosclerosis, diabetes mellitus and demyelinating diseases.

In the course of studies of enzymatic reactions which occur in nerve tissue, it has been felt that a greater insight into neurological function could be obtained if suitable ultramicro procedures could be perfected. Accordingly, a project has been undertaken (NINDB-NC2), and with the use of a liquid scintillation counter, it has been possible to devise a method for a study of the cellular distribution of the enzyme which catalyzes the decarboxylation of glutamic acid to yield the interesting brain constituent γ-amino butyric acid. It is hoped that this technique will be applicable for the study of the formation of other amines such as 5-hydroxytryptamine (serotonin) which has been postulated to be a neurohumoral agent.

Another aspect of research underway in this laboratory is the investigation of the effect of the intra axonal injection of certain key enzymes and materials (NINDB-NC3). It is hoped that by altering the concentration of critical compounds such as acetyl choline or enzymes such as cholinesterase by direct injection of enzymes, substrates, reaction products, or enzyme inhibitors, an insight may be gained regarding the mechanism of nerve conduction. A suitable micro injection technique has been perfected, and a series of experiments has been performed. From these experiments, it appears unlikely that nerve conduction is related to the formation or destruction of acetyl choline or has an immediate dependence upon energy-yielding enzymatic steps of the glycolytic or tricarboxylic acid pathways which are so important for the viability of other tissues. Further experimentation using this technique should yield information to help establish the nature of the process of nerve conduction. Already, the injection of certain amines and derivatives of coenzyme A has been found to exert a profound effect upon the process, and the discovery of the mode of action of these materials should be of considerable neurological significance.

Finally, this laboratory is engaged in a series of experiments in an attempt to elaborate the chemical basis of action of certain drugs which have a profound effect upon the

central nervous system (NINDB-NC4, 7, 10). It is felt that an insight into the nature of the effects of potent psychotomimetic compounds such as lysergic acid diethylamide and tranquilizing agents such as reserpine and meprobamate offer potentially extremely valuable tools for the understanding of chemical abnormalities of mental disease. The pathway of metabolism of lysergic acid diethylamide has been established, and a method has been developed to study the disposition of meprobamate. Examination of the interrelationships between tranquilizing agents and analeptic drugs have yielded preliminary valuable data in studies which are directed toward the elucidation of the chemical reactions involved in anesthesia and narcosis. An interesting ancillary observation is the finding that reserpine can prolong the viability of leukemic mice with concomitant regression of tumors. It is apparent that this particular material which is currently enjoying a formidable vogue in clinical medicine can, under certain conditions, exert a profound metabolic effect, and its administration might have far-reaching effects.

Physical Chemistry. As in previous years, this section under Alexander Rich has continued to study the structure of molecules of biological importance. This program is based upon an awareness that a complete understanding of biochemical function can only be arrived at with an understanding of molecular configuration.

An essential activity of nervous tissue is the transmission of information. How this is accomplished on the molecular level is unknown at the present time. There has, however, been some fragmentary evidence which suggests that the elongated polymeric nucleic acids play an essential role in this activity.

This year a great deal of effort has gone into studying the synthetic polyribonucleotides. These molecules can be made synthetically using an enzymatic system. Both the composition as well as molecular size can be varied at will. Study of these materials is significant in that they are composed of the same chemical units as are found in the naturally occurring ribose nucleic acids (RNA), and they have also been shown to possess the same covalent backbone. Hence, a study of their structure is relevant in that it demonstrates the types of configurations and interactions which are found in the native material.

One of the simplest of these polymers, polyadenylic acid, has been studied by X-ray diffraction. It produces a well oriented fiber photograph which has now been interpreted. This molecule consists of two chains, wound around each other in a helical fashion. These chains are bound to each other

by hydrogen bonds. It is significant that these chains are parallel to each other, in marked contrast to the anti-parallel chains which are found in desoxyribose nucleic acid (DNA).

It has been possible to predict these diffraction patterns through the use of a computing facility which was designed to carry out the necessary mathematical operations.

A most unusual reaction occurs when a purine polymer (polyadenylic acid) is mixed with a pyrimidine polymer (polyuridylic acid). These molecules combine together to form a new two stranded helix, with the bases paired together using hydrogen bonds in a manner similar to that found in DNA. In addition, the backbone chains are on the outside of the helical molecule with a configuration which is not too different from DNA. Using spectrophotometric methods, it has been possible to show that this combination is 1:1 in the two polymeric molecules. This evidence is reinforced by ultracentrifuge studies showing the expected increase in sedimentation constant. This discovery is significant since for the first time it bridges the gap between the two types of nucleic acids, and shows that RNA can assume a DNA-like configuration. This may be of crucial importance in understanding the genetic activity which is associated with RNA.

The effect of various ions on the stability and macromolecular properties of both DNA and RNA have been studied. The effect of magnesium ions is most startling in that at extremely low concentrations this ion has the effect of holding together both types of nucleic acids so that they cannot be easily denatured. The magnesium ions probably act by attaching themselves to the alligned phosphate groups in the molecule, coupling two of these together. It is quite possible that magnesium ions in such low concentrations play an important role in regulating the intracellular activity of the nucleic acids.

In quite a different field, a discovery has been made concerning a complex which forms between a steroid (desoxycholic acid) and a number of amino acids. These form enormously long helical aggregates with a diameter of 40A°. It is of interest to study these since it effectively demonstrates a mode of packing steroid residues. This may in turn be related to the manner in which cholesterol molecules are alligned together within myelin.

Work has continued on the fibrous protein collagen. It has been possible to obtain very well oriented fiber diffraction

photographs which have a great deal of detail. These have been compared with the calculated diffraction pattern which is predicted by the collagen model proposed a year ago. The agreement between these two is very good.

Cerebral Metabolism. This section, under the joint direction of Dr. Louis Sokoloff and Dr. Seymour Kety, is concerned with the nutrition and metabolism of the brain in vivo in man and lower animals. During the past year, two studies in human cerebral circulation and over-all metabolism were completed. In one, it was found that the hallucinatory phenomena produced by lysergic acid diethylamide are not associated with a significant change in the circulation, oxygen or glucose consumption of the brain, suggesting that this hallucinogen acts in some other way than by an interference in the general nutrition or energy production in the brain, mechanisms which are postulated in several current hypotheses of its action. The first series of studies in normal elderly men has shown no significant decrease in cerebral blood flow or oxygen consumption in this group as opposed to previous findings in patients with senile dementia, a finding the definitive interpretation of which must await completion of the collaborative study of which this was one segment.

Dr. Sokoloff's studies on the rapid continuous measurement of blood flow and metabolism in man have continued with their successful application to the effects of certain rapidly acting drugs on cerebral circulation, and to the problem of muscle circulation and oxygen consumption in normal man and in patients with muscular dystrophy.

The technique for the measurement of the local circulation of the brain in the living animal, developed in this section, was applied to the problem of the relationship between circulation and functional activity with rather striking results. In the unanesthetized cat, visual stimulation by means of repetitive light flashes resulted in a reproducible and significant increase in blood flow in those areas of the brain involved in visual function: the visual cortex, lateral geniculate ganglia, and the superior colliculi. This may have some importance as a technique for mapping functionally related portions of the brain.

LABORATORY OF CELLULAR PHARMACOLOGY
Giulio L. Cantoni, Chief

The research activities of the laboratory have developed along three main lines: (1) studies on biological methylation, (2) studies on comparative biochemistry, and (3) studies on the

amino acid metabolism. These three areas have been chosen because they are of importance in basic biochemical research and also because they are central areas having a particular interest to problems of cellular and neuropharmacology. As will be seen from the more detailed analysis which follows, these three areas are contiguous rather than separate, thus affording an opportunity for close intellectual interrelationship and often technical collaboration between the various members of the laboratory. In line with this, it will be found that most of the individual research projects are listed as belonging to more than one of these areas, and it is anticipated that this will continue to be the case even as the laboratory develops and is subdivided into various sections.

Biological Methylation Mechanisms. The major effort of the laboratory in the past year has been expended in this area. The broad significance of transmethylation reactions may be surmized by the extremely wide variety of methylated compounds which are found in nature at all levels of the biological scale. Transmethylation reactions and neogenesis of methyl groups are major biochemical pathways in fungi, plants, invertebrates and all vertebrates. Transmethylation reactions are involved or play a part in the biosynthesis of biologically active substances such as neuro-hormones, acetyl choline and epinephrine, alkaloids such as nicotine, morphineate, etc., and vitamins such as carnitine and probably thiamine. Furthermore, it has been shown that other substances which might be considered as neuro-hormones such as histamine and serotonin undergo biological methylation, though it is not yet clear what physiological role is played by methyl histamine and the methylated derivatives of serotonin.

Transmethylation reactions, inasmuch as they may be considered as the simplest case of transalkylation reactions in general, have features which are of special interest to energy metabolism and cellular transport mechanisms. Of particular relevance to neuropharmacology is the posssibility that transmethylation reactions may be involved in certain special situations or transient conditions of importance in nerve-transmission mechanisms.

Of even more direct relevance to psychopharmacology is the possibility that a relationship exists between trans-methylation reactions and certain types of mental disease. As is generally admitted, it is possible that some types of mental illnesses may be due to a metabolic defect resulting in the formation of a psychosogenic agent. Inasmuch as many of the naturally occurring psychosomimetic agents containing methyl groups linked to a nitrogen, sulfur, or oxygen atom, it

is not unreasonable to propose, as a working hypothesis, that the psychosogenic agent in question may also be a methylated compound.

Stemming from this general background, a variety of specific problems are being attacked in the laboratory ranging from the very basic studies on the mechanism of action of the methionine activating enzyme (NIMH-CP3 and 4) to the more applied program which is carried out in collaboration with Dr. Butler of the Laboratory of Clinical Science (NIMH-CP2). Other projects which stem from this general line of approach are NIMH-CP1, 5, and 6.

Comparative Biochemistry. The relationship of comparative biochemistry to cellular pharmacology is the cornerstone of the scientific philosophy of this laboratory. There has been a tendency in the last fifteen years to overemphasize the concept of the unity of biochemistry. This concept has been largely based on the discovery that the living cell utilizes certain basic reaction patterns for the fulfillment of its metabolic needs. These reaction patterns are similar and in many cases identical for cells as far apart as E. coli and brain cells. The concept of the unity of biochemistry has been most fruitful and stimulating, and undoubtedly has been responsible for much biochemical advance; it now stands as one of the fundamental facts of modern science. However, this fundamental fact needs to be reconciled with the equally fundamental fact that different cells and different tissues exhibit a whole gamut of responses to the administration of chemical agents and drugs. The rational approach to an understanding of the reasons for these varied responses lies in a systematic long-range study directed at the understanding of the metabolic differences between different tissues and different species. Such an approach is not one which can be developed quickly, rather it is planned to build in this direction slowly over the course of the years, in the main, utilizing as building blocks the projects which arise from more defined areas. Projects NIMH-CP3, 4, 5, 7, 8 and 9 each contribute in different measure toward this end.

Amino Acid Metabolism. A study of the intermediary metabolism of amino acid and of proteins offers great possibilities for contributions at the basic level of biochemical research and for the development of a program on cellular regulatory mechanisms. It has become increasingly clear in recent years that many among the physiological cellular regulators are derived directly from amino acids (neurohormones, polypeptide hormones, and plant hormones). The problems of protein synthesis and protein structure are among the most important in biology and fundamental to a better

understanding of enzymic catalysis. Studies on the metabolism of amino acid are also related to comparative biochemistry because one of the characteristic features of mammalian metabolism as opposed to the metabolism of lower species is the relative inability of the mammal to synthesize amino acids. Finally, studies in the areas of amino acid metabolism are of particular interest to mental health since in numerous mental and neurological diseases there is evidence of derangement in the metabolism of amino acids. Nowhere is this seen more clearly than in the disease, phenylpyruvica oligophrenia, which is characterized biochemically by the excretion of phenylpyruvic acid, an abnormal metabolite derived from phenylalanine. It is noteworthy that Dr. Kaufman's studies in this area have advanced to the point where, by applying what has been learned at the fundamental level to the more specific problem of oligophrenia phenylpyruvica, it is hoped to contribute significantly to the understanding of the etiology of this form of mental retardation. The projects which contribute to this area are NIMH-CP3, 4, 5, 6, 7, 8, and 9.

ADDICTION RESEARCH CENTER
Harris Isbell, Chief

Addictive Properties of New Analgesics. Testing of new pain-relieving drugs for addictive properties is a technological project which is carried on primarily for the protection of the public, with the object of preventing the introduction of potentially addicting substance into uncontrolled clinical use. Drugs are referred to the Center by the Committee on Drug Addiction and Narcotics, National Research Council. After the addictive potentialities of these new drugs have been determined by the methods described in previous annual reports, the findings are sent to the Committee on Drug Addiction and Narcotics, NRC, who in turn informs the Section on Addicting-Producing Drugs, World Health Organization. These bodies then advise the U.S. Government and the United Nations concerning appropriate legal action connected with the control of these drugs at national and international levels.

During the year, fourteen new analgesics were tested. Eleven of these proved to have addiction liability of some degree; three were found to be devoid of addictive properties.

No changes are contemplated in the testing program during the coming year. Since it is felt that the synthetic chemical and biologicalapproaches, which have been used heretofore in developing new analgesics, automatically select drugs with morphine-like addiction liability, attempts will continue to persuade the pharmaceutical chemists and pharmacologists to

change their approaches. Studies will continue on opiate antagonists as analgesics, particularly with reference to relief of chronic pain and tolerance.

Chronic Barbiturate and Alcoholic Intoxication. Analysis of more extensive data has been completed and confirms the impression previously reported that abstinence after chronic ingestion of 0.4 gram or less of these barbiturates daily is clinically insignificant. This particular experiment unequivocally demonstrated that considerable tolerance to "low" doses of barbiturates can be developed. Furthermore, despite such tolerance, abstinence is quite mild.

Studies on the equivalence of chronic barbiturate and chronic alcoholic intoxications in dogs were continued by attempting to substitute alcohol for barbiturates in chronically intoxicated animals. If alcohol suppressed, wholly or in part, the expected symptoms of abstinence from barbiturates, it would be surmised that these two intoxications were to some degree equivalent, just as addiction to meperidine is partially equivalent to addiction to morphine. Substitutions were carried out in five animals. Following withdrawal of alcohol after two weeks or more of substitution for barbiturates, none of the dogs had convulsions and only one had a severe delirium. Twelve additional dogs are now being readied for substitution of alcohol. These experiments will be continued until substitution of alcohol for barbiturates has been accomplished in a sufficient number of animals to give a definitive answer to the question of the possible equivalence of the two drugs. It will be extended to include determination of the possible equivalence of intoxication with chloral and paraldehyde to intoxication with barbiturates. Eventually, it is hoped to study the treatment of delirium tremens and " rum fits" in animals, with particular reference to reserpine, chlorpromazine, and meprobamate. Since there is suggestive evidence that meprobamate may induce a type of physical dependence resembling that caused by alcohol and barbiturates, both clinical and animal studies will be initiated with this substance.

Intoxication With Drugs Other Than Opiates, Alcohol, and Barbiturates. This particular project deals primarily with the psychosomimetic drugs and the "tranquilizing" drugs. Experiments are carried out in the hope of shedding light on some of the mechanisms of action of these drugs and on possible relationships to the etiology of the major psychoses.

Work showing that reserpine made the LSD-psychosis worse rather than better was completed and a paper has been prepared on this subject. Azacyclonol, administered intravenously, failed to reverse the LSD-psychosis, just as it

failed to prevent it. A number of other psychosomimetic drugs were studied during the year. Extensive experiments were carried out with bufotenine, an indole compound which induces effects resembling those caused by LSD in monkeys, and which causes depression in the lateral geniculate of the cat, similar to that caused by LSD. When the drug was given intramuscularly, definite effects appeared after 10 to 12.5 mg. for each 70 kg. of body weight. These effects appeared very rapidly, being noticeable in one to two minutes, reaching peak in 15 to 30 minutes, and declining in one to one and one-half hours, The "objective" effects were referable chiefly to the cardiovascular system. Bufotenine causes sharp elevation in systolic and diastolic blood pressures; the diastolic pressure is elevated somewhat more than the systolic. The drug induces sinus arrhythmia and bradycardia, with low nodal rhythms in some patients. At the height of the reaction, patients may show a peculiar bluish-red cyanosis of the face and neck. The cardiovascular effects of bufotenine appear to resemble the cardiovascular symptoms occurring in carcinoid, in which high blood-serotonin levels are present. Subjective effects induced by bufotenine are, in part at least, attributable to the cardiovascular effects. They include a tingling beginning near the injection site and spreading over the entire body, a sense of constriction in the chest, feeling of "a tight band around the head," nausea, anxiety, dysphoria, sweating and dyspnea. The mental symptoms include "confusion" and perception of colored lights and patterns which do not form definite pictures or objects. Disorientation, depersonalization, derealization, and visual perceptual distortion were not observed with the doses used. The chief resemblance of the bufotenine reaction to the LSD psychosis was perception of colored lights and patterns.

Studies of Ololiuqui, a crude drug consisting of the seeds of a morning glory which grows in Mexico and the Caribbean area, were also carried out. As much as 5 to 7 grams orally of the ground seeds caused very few subjective sensations. No distortion, depersonalization, perceptual distortion nor hallucinations were observed. The chief subjective sensations reported were nausea, abdominal discomfort and sleepiness. The drug did dilate pupils, increase blood pressure, and enhance the deep tendon reflexes.

As much as 60 mg. of serotonin creatinine sulfate intramuscularly caused very minor cardiovascular changes, but no mental changes of consequence.

Oral doses of 250 to 300 mg. of Ibogaine, an indole derivative of the root of a plant indigenous to Africa, induced a psychosis resembling the LSD-reaction. The phenomena

observed included dilatation of pupils, elevation of blood pressure, accentuation of deep tendon reflexes, feelings of depersonalization, and optical hallucinations. Sufficient data are not yet available to define the characteristics of the Ibogaine reaction completely.

Studies with these interesting psychosomimetic agents will be continued during the coming year. Some contributions are hoped for to theories which relate LSD-effects to excess or deficiency of serotonin, and to determine whether the development of entoptic phenomena (visual hallucinations) are correlated with depression in the lateral geniculate body. This is to be done by studying indole derivatives which cause, or do not cause, such depression in the geniculate. Attempts will be made to block or reverse the LSD-reaction with serotonin antagonists, such as BAS, with continued exploration of the possible use of the LSD-psychosis as a screen for new tranquilizing drugs.

Biochemistry of Addiction. It is hoped to transfer major effort in this field to the effects of chronic intoxication with various drugs on the cellular chemistry of the nervous system.

The project dealing with the clinical endocrinology of opiate addiction was completed during the year. New information includes depression of 17-hydroxycorticoids in blood and urine during maintained addiction with morphine, followed by marked elevation in blood and urine on withdrawal. Infused hydrocortisone disappears from the blood at the usual rate during maintained addiction. This finding excludes a lessened rate of metabolism or excretion of 17-hydroxycorticoids as an explanation for low serum and urine levels during addiction. ACTH induces the same degree of elevation in addicted persons as in nonaddicted persons. This reinforces the idea that morphine causes a block at the pituitary level rather than at the adrenal or gonadal level.

No definite changes in the excretion of the chief metabolite of serotonin, 5-hydroxy-indole acetic acid, occurred during maintained addiction to or withdrawal from morphine. Similar studies are to be made during chronic intoxication with other drugs.

During the coming year studies will be made on the effects of a number of drugs on adrenal and gonadal functions. The drugs scheduled for experimentation include barbiturates, chlorpromazine, reserpine, meperidine and cocaine. It is hoped to develop methods adaptable to human clinical work which will permit us to study the degradation, distribution and excretion of drugs of interest to the Center.

Neurophysiology and Neuropharmacology of Addiction. Dr. Abraham Wikler in charge of this program was largely concerned throughout the year with the preparation of a review on "The Relation of Psychiatry to Pharmacology", which is believed to be the most definitive analysis of the literature in this field yet made.

Massive doses of chlorpromazine (50 mg./kg.) induced stiffness and tremor in monkeys, but tremors of the "cog-wheel" type were not observed, so that the resemblance to Parkinsonism is not complete. Monkeys receiving such large doses of chlorpromazine developed spontaneous seizures and bizarre behavior suggesting hallucinations.

During the coming year studies on the neurophysiology of barbiturate intoxication will be continued, utilizing dogs. It is hoped to expand the program to include determinations of acetylcholine, cholineacetylase, and cholinesterase in spinal fluid and tissue. Since convulsions are reported to occur following withdrawal of meprobamate after chronic intoxication, animal work with this agent will be initiated. It is also hoped to begin studies on the conditioning of "pharmacological" dependence in rats, and to explore further the effects of some of the psychosomimetic drugs on the electroencephalogram.

Psychology of Addiction. The Psychological Section collaborated in the studies on chronic intoxication with low doses of barbiturates, which were described above. A beginning was made on the development of inventories for distinguishing the subjective effects of various classes of drugs. One such inventory clearly differentiated between the effects of the marihuana-like drug and placebo. A substantial number of inventory questions which may reflect the actions of and differentiate between morphine, pentobarbital, and LSD have been gathered. Work on the conditioned inhibition of the feeding response in rats was enlarged to include measures of the effects of drugs on unconditioned bar-pressing and time-action curves. These data have yielded patterns of effects which clearly differentiate between potent analgesics, hypnotics, and "tranquilizers".

During the coming year the psychological section will investigate further possible relationships between personality characteristics and addiction by comparing addict physicians with other equated groups. It will continue with the development of inventories for distinguishing various classes of drugs, especially the opiates. These inventories are badly needed since they would provide a quantitative way of measuring subjective effects of these drugs, which currently are not available. Complementary studies in both man and animals

designed to further elucidate psychological mechanisms of action of morphine and pentobarbital will be undertaken.

LABORATORY OF CLINICAL SCIENCE
Edward V. Evarts, Acting Chief

The general program goals of the Sections on Biochemistry and Pharmacology of the Laboratory of Clinical Science, which constitute the basic research sections of this laboratory, are an elucidation of the biochemical and pharmacological correlates of disturbances of behavior. A general goal such as this allows for a wide variety of specific research activities, which range in character from fairly basic studies of the cellular mechanisms involved in biochemical or pharmacological processes to what might be called studies on applied biochemistry and pharmacology.

Biochemistry. The work of this section has included both basic and applied biochemical research. In the area of basic biochemical research may be included the studies concerned with experimental allergic encephalomyelitis. These studies are directed toward the problem of identification and characterization of the immunologic and biochemical changes associated with this experimental disease process. Individual projects in this area have been directed to an isolation of the antigen responsible for allergic encephalomyelitis and to the characterization of the abnormal lipids and proteins which appear in the blood of encephalitic animals. Studies are being directed to determining the degree to which allergic processes are actually involved in the encephalomyelitis which results from administration of brain tissue to experimental animals. The Section on Biochemistry has also carried out studies on the antidiuretic effects of LSD in normal and schizophrenic subjects. This project is part of a program directed to determining the biological correlates of the experimental psychosis which is produced by LSD.

Progress has been made in studies of the nature of the antigen which is responsible for experimental encephalomyelitis. Dr. Kies and her co-workers have obtained evidence that the antigen in question may be a soluble glycoprotein which is completely free of lipid material. This finding is in contrast to the findings of previous investigators who have concluded that the active antigen was a proteolipid. Dr. Kies has also further characterized the abnormal lipids and proteins which appear in the sera of encephalitic animals. In another group of studies, Dr. Kies has found that LSD, when administered in doses of 100 μg. to normal subjects, causes a marked though transient antidiuretic effect.

Pharmacology. The work of this section also ranges from basic studies of pharmacological mechanisms to studies with direct clinical significance, such as those involving determinations of the physiological disposition and metabolic fate of phrenotropic agents in man. The work of the Section on Pharmacology may be divided into three general areas. The first of these areas includes studies aimed at a further understanding of the biochemical factors involved in the development of tolerance to narcotic drugs. In this project, Dr. Axelrod and Dr. Cochin are investigating the effects of narcotic drugs on enzymatic mechanisms in experimental animals. Concurrent observations on the behavioral effects of narcotic drugs in these animals allow correlation of the effects of the narcotic drugs on enzyme systems with the effects of these narcotic drugs on behavior. In another area of research, Dr. Axelrod, together with a group of co-workers, is conducting a series of studies concerning the physiological disposition and metabolic fate of drugs affecting the central nervous system. This work is valuable both from the standpoint of basic pharmacological information and also as a source of information which is of value in the clinical use of the drugs under investigation. Within this project, a number of drugs, including LSD, papavarine, and meprobamate have been studied. A third series of studies in this section may be included under the general title of cellular mechanisms involved in the metabolism of drugs. In this research area, Dr. Axelrod and a series of collaborators have studied the cellular mechanisms involved in the metabolic transformation of LSD and papavarine. Studies on glucuronide synthesis have also been carried out. These studied on glucuronide synthesis are relevant to the metabolic transformation of a large number of pharmacological agents.

Dr. Axelrod and his collaborators have determined the metabolic fate of LSD, in vivo, and have characterized the enzyme systems which participate in the metabolic transformation of LSD. It has been shown that 2-oxy-LSD, the metabolic product of LSD, in vivo, does not have psychological effects in man or neurophysiological effects in experimental animals. The elucidation of the enzymatic mechanisms involved in the transformation of LSD provides a possible clue to investigations of possible defects of enzymatic processes in psychotic patients. One might speculate that if an excess of some hallucinogenic substance were involved in psychoses, alterations in the activity of the enzyme systems which detoxify the hallucinogenic substances might be reflected in behavioral changes of the patients who suffer from the psychosis. This speculation indicates the possible application of the type of studies that Dr. Axelrod is carrying out to the clinical problems of mental health. Dr. Axelrod's observations on the marked decrease in

the activity of enzymes which N-demethylate narcotic drugs in animals which are tolerant to narcotic drugs is an original contribution of considerable importance in our understanding of the phenomenon of tolerance to narcotic agents.

Several of the findings which have been cited in the previous sections of this summary may reasonably be described as outstanding accomplishments. The first of these would be Dr. Axelrod's observations on a decrease in enzyme activity in association with tolerance to narcotic drugs. This finding is in a way surprising, since it had been commonly supposed that there was an adaptive increase of enzyme activity in association with the tolerant state. Dr. Axelrod's data, however, show conclusively that there is an inverse relationship between degree of tolerance and activity of those enzymes which N-demethylate narcotic drugs. On the basis of this finding, Dr. Axelrod has speculated that the ease of access of narcotic drugs to enzymes (as indicated by the enzymatic activity) is, so to speak, a mirror of the accessibility of the narcotic drug to the pharmacological receptor site. In other words, Dr. Axelrod suggests that, with tolerance, there is an inactivation both of the receptor site at which the drug exerts its pharmacological effect and of the enzyme which N-demethylates the narcotic drug in question. This finding would seem to be of fundamental importance in further studies aimed at clarifying the mechanisms of tolerance to narcotic drugs.

Another outstanding accomplishment may be seen in Dr. Kies' finding concerning the nature of the antigen which is responsible for allergic encephalomyelitis. As the result of extremely careful and painstaking work carried out in a great number of experimental animals, Dr. Kies has succeeded in establishing that lipid free extracts of brain have the capacity to cause allergic encephalomyelitis. This finding is an original observation and is one of the foremost contributions made in recent years to the field of allergic encephalomyelitis. Dr. Kies has further demonstrated that the lipid free material which causes encephalitis is probably a glycoprotein. Further studies will be aimed at more specific characterizations of the nature of this active material.

LABORATORY OF PSYCHOLOGY
David Shakow, Chief

Since the last annual report the Laboratory of Psychology has reached a reasonably satisfactory degree of stabilization even though the major personnel problem, that of the appointment of Chiefs for the Sections on Personality, and Learning and

Perception, has not as yet been solved. In the basic area of this combined laboratory are the three sections on Aging, Animal Behavior, and Learning and Perception.

Aging. The purpose of this section is to conduct research on aging of the nervous system. The goal of this research is an understanding of the factors governing the changes in function and structure of the nervous system which occur with age. This basic knowledge is necessary in the development of rational methods of prevention or reduction of the problems of aging. Research experience has shown the difficulty of compartmentalizing the problems of aging according to conventional academic divisions. The Section on Aging has been of national influence in helping to define the problems of the field and to secure some agreement about the focal points for research. The presence of different points of view within the section has been most helpful in "blocking out" the problems. There now clearly exists the basis for organizing research and scientific opportunities in aging and also a basis for optimism that the research will benefit individuals through the influences which research findings will have upon mental health practices.

This is the fifth year of the organization and function of the Section on Aging, although not in its present form, of course. It has continued the plan of developing research projects on aging of the nervous system by several scientific disciplines or approaches. The major contributions of the Section on Aging during the past year were: (1) In a series of studies, James Birren and Jack Botwinick obtained evidence that the slowing of responses with increased age is primarily a property of the central nervous system. This work received a Ciba Foundation award as a contribution to the experimental study of aging; (2) Jack Botwinick has found that elderly subjects require a longer time to prepare for a response than do young subjects. In studies of the role of motivation in the long response latencies of the elderly, Jack Botwinick found, under conditions of electric shock motivation, both the elderly and the young improve or speed-up to the same extent; (3) Joel Garbus and Eugene Weinbach demonstrated that liver tissues from old rats show a decline both in respiration and phosphate esterification with age; (4) William Bondareff has been surgically removing minute quantities of nervous tissue from living rats of different ages to study age changes in cells of the nervous system and has successfully prepared frozen-dried nervous tissue for cytological studies; (5) Eugene Streicher has continued his development of sensitive micro-methods for the measurement of electrolytes in minute samples of nervous tissues; (6) In his studies of age changes in timing of psychophysiological processes, Alfred Weiss found that the

electrical response latency of the eye does not vary with age. Electromyographic measurements of young and old during simple auditory reaction time studies showed only small age differences in timing or peripheral events, thus strengthening the general finding of the laboratory that the major changes in expectancy and response latency are a function of the central nervous system.

Animal Behavior. Considerable attention has been given during the year to determining the neural structures involved in the impairment of problem-solving behavior which follows frontal lobotomy, or other damage to the frontal lobes.

Such impairment has been demonstrated conclusively in monkeys, but has not been shown in man. The results of the experiment conducted on chimpanzees indicate that immediately after operation they show effects identical with those seen in monkeys (delayed alternation but not discrimination deficit), but that unlike monkeys they are able to improve their performance to equal their preoperative performance. Thus, at the end point of the experiment, they, like humans, show no clear cut deficit in problem-solving behavior. This is a significant finding in that it reconciles the disparate results of two other studies and in that it would question those interpretations of man's success on these tasks after surgery as being entirely dependent on his high level of verbalization. The evidence suggests instead some substantial difference in the neural organization among these three primates.

Delayed alternation performance, but not discrimination performance, is impaired following injury to the frontal lobes of monkeys. It had been demonstrated that this impairment follows damage to the dorsolateral cortex, but not damage to the thalamus, i.e., the nucleus from which this cortex receives projections. Another line of investigation suggested that the head of the caudate nucleus must be intact for the animal to be proficient in problem solving. Accordingly, a series of 14 monkeys was subjected to electrolytic lesions of the head of the caudate and structures around it. The histology on these animals is already available and indicates that the impairment in problem-solving behavior does indeed follow damage to the head of the caudate nucleus. This finding suggests that there might be connections between the caudate and the frontal cortex (not yet demonstrated) or that the head of the caudate itself serves functions related to problem-solving behavior, functions not generally associated with structures of the corpus striatum. Lesions placed elsewhere suggest that the fornix system may also serve functions related to problem-solving behavior.

In general, these studies clarify some of the issues concerning the relationships between brain function and problem-solving behavior, but pose other issues which, when resolved, will enhance our understanding of how the brain handles problem-solving tasks.

The social behavior investigations this year have necessarily been curtailed because of the moving from Building 14 to Building 9 and the delays involved in setting up cages, equipment and facilities. However, six groups of monkeys have been studied as part of the investigation of the interaction of the effects of amygdalectomy and post-operative experience in monkeys and the results to date appear to indicate that the effects of the surgery on post-operative social behavior may be different depending on the differences in immediate post-operative experience of the animals. It should be noted that the amygdala lesions have been produced successfully by the stereotaxic instrument, thus eliminating the necessity for the difficult and traumatic direct surgical approach to the amygdala. The effect of three different types of lesions on social behavior in chimpanzees has been under investigation. The results so far suggest that unilateral temporal lobe lesions may have some effect, but that bilateral prefrontal lobotomy results in a profound, if temporary, depression in dominance.

The primary investigation with epileptic subjects has been a comparison of several clinically different (particularly with reference to the EEG) epileptic groups on a battery of psychological tests. This study has involved approximately 100 patients and on the order of 250 patient hours. Information on some 70 of these patients has been analyzed and the data are being prepared for publication. The results of this analysis suggest that "memory", and "attention" tests discriminate among various epileptic groups, but that the groups do not rank in the same order on the two kinds of tests. A particular emphasis in this investigation has been the use of the Continuous Performance Task. This instrument has now been shown to be capable of discriminating among epileptic subpopulations and a new version of it is now under construction. This new version will permit extensive and precise stimulus control as well as simultaneous polygraphic recording of the EEG and the behavior of the subject. This instrument should prove to be extremely versatile for the investigation of many visual and auditory functions, alone and in relation to the EEG. Other studies with the epileptic patients have been designed to investigate specifically losses of function which parallel those shown in experimentally brain-damaged monkeys.

Two studies have been completed with normal controls, one other is in the process and a fourth is now in the planning stage. These investigations have dealt with the effects of centrally-acting drugs on Continuous Performance and have been designed to aid in the specification of the brain locus and functions involved in this test. To date, these studies have involved 27 subjects, approximately 200 subject hours and four drugs (chlorpromazine, secobarbital and meperidine). The study being planned will extend the information to three other drugs: meprobamate (Miltown), phenobarbital, and amphetamine. To date the results indicate that only chlorpromazine has a significant deleterious effect on the C.P.T. and that the effect is greater with higher doses of chlorpromazine. Several other drugs have had no effect even when tested at the period of their maximum activity. The chlorpromazine effect is not due to pupillary constriction, as demonstrated in an investigation of the effects of an artificial pupil on the C.P.T.

Perception and Learning. The section is engaged in a program of research aimed broadly toward the study of behavior as a function of (a) structure of the immediate environment, (b) capacities of the organism for perceiving environmental stimuli, (c) capacities of the organism for altering its responses to stimuli through learning, and (d) gross physiological state of the organism. More specific approaches are represented by the several investigators. On the one hand, the major interest lies in how perceptual processes develop through learning and are affected by the physiological state of the organism (Dr. Blough and Dr. Carlson) and, on the other hand, in how hereditary and environmental factors operate in the determination of learned behavior and physiological functioning (Dr. Calhoun).

Dr. Carlson is concerned chiefly with the influence on human perceptual response of the immediate state of the individual, defined in terms of emotional state, drug condition, or preceding experience. He plans to increase the scope of assessing the immediate state of the individual by including measures of responses of the autonomic nervous system, and he is also working on a method for analyzing sequences of stimuli and responses. Current work is in terms of assessing the effects of certain drugs, primarily LSD and chlorpromazine, on human visual functions. The finding here of primary interest during the year is that individual pupillary reactions to the drug conditions studied appear to be highly reliable, and individual differences in pupillary response may even be consistent and meaningful under conditions which produce no average pupillary effect over all subjects.

Dr. Blough's general interests lie in studies of stimulus differentiation, concept formation, and conditioning, oriented toward identifying basic mechanisms of perceptual and thought processes. His present work is concerned with identifying basic sensory mechanisms in visual discrimination and discrimination learning, using the pigeon as an experimental animal and a new conditioning technique worked out by Dr. Blough. Among the interesting results of these studies during the past year are the following: (a) The drug LSD raised the pigeon's absolute scotopic threshold substantially but improved performance on a discrimination test, (b) the pigeon appears to use overt responses to "remember" stimuli in a delayed matching task, and (c) an anomaly was discovered in the pigeon's dark adaptation at 700 m^{u}, which may be the result of mutual inhibition among retinal receptor elements.

Dr. Calhoun is engaged in organizing a broad program of animal research designed to study the interaction of heredity, environment, and early learned behavior on later expressions of physiological function and individual and social behavior. A large dairy barn facility in Rockville has been obtained for this project, and extensive modifications of the barn and development of special equipment are currently underway. This past year Dr. Calhoun has been concerned with analyzing the behavior of rats in terms of variables such as density and contact rate of the animals and kind, frequency, and structure of stimulus objects in the environment. He has found that the frequency of several types of spontaneous behavior is a function of the duration of the behavior, and the relation may be described by a negative exponential curve. Each behavior has its own characteristic curve, which in some cases is modified by age and heredity.

LABORATORY OF SOCIO-ENVIRONMENTAL STUDIES
John A. Clausen, Chief

The program of the Laboratory of Socio-environmental Studies entails research on social, cultural and, to some degree, genetic and demographic phenomena as these relate to mental health and to the etiology, diagnosis and treatment of mental illness. The laboratory staff consists of sociologists, social psychologists, and social anthropologists. Research in process ranges from the intensive examination and analysis of social development within the family setting to studies of the mental hospital as a social system and epidemiological studies in large communities. The laboratory's goal is to develop systematic research into those aspects of social organization and interaction which bear most critically upon personality development and psychopathology, seeking continuity in project sequences rather than a comprehensive program. The organization of the several sections is, however, intended to encompass

the full range of sociological and anthropological approaches to mental health research.

The application of social science theory and methodology to the mental health field is, on the whole, a recent development, though descriptive studies of the social process of personality development have a much longer history. Much basic work must be done in the line of conceptualization and taxonomy of relationships and group structures as a prelude to the analysis of interrelationships significant to mental health. Data collection, whether by observation or by interview, tends to be exceedingly consuming of time and may be subject to a variety of types of bias or contextual influence which must be continually assessed. The program of the laboratory is designed both to tackle these basic methodological problems and to bring to bear in interdisciplinary projects the tested theories and demonstrated methods thus far evolved in the social sciences.

Early in 1956 there developed opportunities for collaboration with personnel of other laboratories in projects on the aging process and on schizophrenia which required sociological and social psychological skills. As a consequence, some shift in emphasis from that envisioned at the end of the previous year has occurred. The major projects thus affected were the two which comprise a long term study of the adaptation of patient and family to mental illness, which has been scheduled to enter a new phase of data collection this past year. Work on these projects has been considerably curtailed. At the end of 1955 a series of articles, comprising an entire number of the Journal of Social Issues, had reported progress on this study to date. While these articles constituted only a preliminary and partial report of the data, their preparation afforded a convenient opportunity for review and rescheduling of the program of research with families so that some of its staff could temporarily be allocated elsewhere. The time available for these projects during the current year has been applied to work on methodological issues relating to further, more efficient data collection and to the analysis of segments of data previously collected. Parenthetically, it appears that the previously published findings of this research have had a substantial impact on the social service operations of a number of mental hospitals and have served to stimulate a considerable increase in research interest on other aspects of the impact of mental illness.

Social Developmental and Family Studies. This section, under the direction of Dr. Marian Radke Yarrow, engages in research on social psychological aspects of human development. The research is formulated in age-developmental terms, from

childhood through old age, and in terms of the influence of significant groups, such as the family, upon the course of individual development throughout the life span. A central theoretical focus in the research is upon the interaction of socio-cultural variables and individual psychological factors.

Problems of special interest in current research efforts concern the nature of a critical developmental period, namely, old age, including the individual's response to the stresses of this period and the influences of societal expectations and requirements in this age period. Basic problems of child development are also now being studied. These concern the child's development of self identity, and his awareness and sensitivity to the psychological and social characteristics and motives of others.

During 1956 the major new developments in the work of this section consisted of expanded participation in two projects involving collaboration with other laboratories of the Institute, one on the study of human aging and the other on the problem of self identity in siblings of multiple births (identical schizophrenic quadruplets). The designs and techniques of these projects were fully worked out during the year. Data collection proceeded and will continue through 1957. In both projects, data analysis is being carried on concomitantly with data collection.

Considerable progress has been made in analyzing the voluminous data secured during 1955 on children's social perceptions and peer relationships. This very basic study of developmental aspects of interpersonal perceptions and interaction should yield a number of papers during 1957 which will add significantly to understanding of the role of psychological and socio-cultural factors in shaping the way children perceive, evaluate and respond to others.

During 1957 it is likely that the research on aging will be expanded, probably to include comparisons between the healthy subjects thus far studied and a group of hospitalized, senile patients. Primary concentration will be given to the analysis and the reporting of findings from the projects on child development described above. The only new activity envisioned is the beginning of a program of studies of juvenile delinquency if an appropriately experienced staff member can be recruited.

Community and Population Studies. This section, under Dr. Melvin Kohn, studies the relationship between broader aspects of the social order and mental health or illness, also

incorporating where possible consideration of genetic factors. The long range program includes: epidemiological research on mental illness and on behavior pathologies such as drug addiction and delinquency; study of the processes by which mental illness is recognized or defined and the channels through which it is brought to treatment (whether by formal therapeutic agents or other means); and basic studies of community organization, social structure or cultural dynamics as prerequisites to achievement of these previously mentioned aims. The central focus of research conducted to date has been on social and cultural factors associated with schizophrenia.

Following earlier research which showed a relationship between socio-economic status, parental authority behavior, and schizophrenia in a relatively homogeneous population in a Maryland city, present efforts have been directed toward securing a more adequate knowledge of the structuring of family relationships in different socio-economic strata of the general population. During 1956 a study comparing middle class to working class families was designed, pretesting of schedules was completed, and interviews obtained with 86 per cent of the designated sample of 300 mothers. In another 100 families, mother, father, and ten-year-old child are being interviewed, using pairs of interviewers who interview the parents simultaneously but separately, thus assuring independence of reports, and then interview the child. This study should aid in the designation of critical variables for control in subsequent studies of social factors in schizophrenia.

Analysis and reporting of a field study of public response to the threat of polio in an epidemic area provided an illustration of a public health problem with mental health overtones. It was found that a relatively small proportion of parents--about 15 per cent--who were particularly anxious about polio, were able to influence local school officials to such an extent that schools were closed against the advice of public health officials. Such studies will be undertaken from time to time, in so far as they afford opportunities to extend our knowledge of human response to extreme situations.

The staff of this section contributed both to the studies of families of hospitalized patients, mentioned above, and to research on the wards of the Clinical Center. Exploratory work was begun on the influence that the social setting within which tranquilizing drugs are administered has on drug effects. Further work along this line is envisioned as part of a collaborative project at Saint Elizabeths Hospital.

Dr. Gordon Allen returned from his four year assignment to the New York State Psychiatric Institute to provide consultation on genetic aspects of several projects and to continue the analysis of data secured in his twin study of mental deficiency.

Social Studies in Therapeutic Settings. Studies of the patient's adaptation to the hospital world and of the implications of various staffing arrangements for achievement of therapeutic objectives have been a part of the laboratory program for several years. The support of such studies through the budget of the Clinical Investigations Branch had not, however, been possible prior to fiscal year 1957. Therefore, most of the research thus far undertaken in this field has been done by members of the other two sections of the laboratory.

A series of setbacks in staffing plans, largely attributable to the competition of our own grant programs, has delayed program development in this area. There are few well trained social scientists who possess real familiarity with the milieu of the mental hospital, and these are in great demand. Present recruiting efforts aim toward appointment in June of several promising persons who are currently completing their Ph.D.'s. Unfortunately, the outlook for more senior staff is not bright, so a period of in-service training for such personnel must be anticipated.

No new projects were undertaken during 1956, but a substantial amount of staff time was given over to collaborative work with other units of the Clinical Investigations Branch in seeking to design studies of treatment milieux. In addition, Dr. Goffman completed field work at Saint Elizabeths Hospital in his study of the social life of the mental hospital patient. Data analysis and preparation of a series of reports are in process. Transferred to the new section was Dr. Jordan's project applying systematic behavioral observation to the study of acting-out child-patients in the classroom situation on Ward 4-E of the Clinical Center. Preliminary analyses suggest that the techniques developed, while somewhat costly to apply, may permit reasonably objective measurement of a number of dimensions of patient behavior in the treatment setting. The work with children will continue, and the observational techniques, coupled with staff reports on patient behavior, will be extended to the study of the structure of the therapeutic milieu on a ward for psychotic adult patients.

The phasing of the laboratory's program finds 1956 with less to report in the way of findings than in the previous year's report. Laboratory staff made several significant contributions to the scientific literature of their disciplines,

however, apart from the projects to which the bulk of their time was allocated.

Laboratory staff likewise contributed to planning or presented papers at several major conferences dealing with mental health research and theory--the Joint Conference on Pharmacotherapy in Psychiatry, the Josiah Macy Jr. Foundation Conference on Group Processes, the Milbank Memorial Fund's Conference on the Nature and Transmission of the Genetic and Cultural Characteristics of Human Populations, and the Fifth Annual Seminar, Reintegration of the Patient into the Community, at the Roanoke Veterans Administration Hospital.

Major tasks of recruitment and of administrative and research planning lie ahead in establishing the community study (conceived as a joint operation of several branches and laboratories) provided for in the current year's budget. Beyond this, primary efforts will be directed to research in process rather than to the development of new studies.

SECTION ON TECHNICAL DEVELOPMENT
Michael M. Davis, Jr., Chief

During the latter part of the year, the section moved its entire facilities to new and somewhat larger quarters which will make it a somewhat more effective and safer operation. Although the section spends a considerable fraction of its time in the repair and maintenance of existing equipment in the various laboratories and in providing many central services such as electronic stock room, a loan service of specialized equipment, and an indexed file of latest instruments and equipment available nationally, its main contribution to the research program has been in its primary function of the design, development, and construction of new research instruments, in collaboration with investigators from the various laboratories. Among the instruments or techniques presently under development are techniques for the fabrication of quartz micropipettes, the development of a data analyzer coupled to a microfilm reader, and the application of transistor circuits to a wireless intercommunication system for use in the neurosurgical operating room. Among instruments developed in the course of the past year are a complex and very flexible psychometric apparatus adaptable to a variety of psychological timing measures and designed so that its outputs can be fed to automatic data processing equipment. An automatic centrifuge starter was developed to reduce significantly the time spent by investigators in manually adjusting the transformer output of super-speed centrifuges and to provide reproducible, higher, and more even centrifuge acceleration

rates. The section developed, for the Laboratory of Neuroanatomical Sciences, a simple apparatus which makes possible nearly errorless counting of randomly dispersed objects in a large field. The present intercommunication system for the neurosurgical operating room, developed by Michael Davis in collaboration with Maitland Baldwin, was described in a paper presented at the national convention of the Institute of Radio Engineers, and a description of the automatic centrifuge starter will appear in a forthcoming issue of the Review of Scientific Instruments.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-B-1
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Biophysics
LABORATORY

4. _____
SECTION

5. Bethesda, Md.
LOCATION

6. Ionic Permeabilities of the Squid Giant Axon Membrane.
PROJECT TITLE

7. Moore, J. W., Cole, K. S.
PRINCIPAL INVESTIGATORS

8. Taylor, R. E.
OTHER INVESTIGATORS

9. NINDB-NP-3 and NIMH-NP-2

10. PROJECT DESCRIPTION:

Objectives: The interpretation of nerve function in terms of fast ionic transports and the elucidation of the structures and mechanisms by which these transports are controlled.

Methods Employed: The instrumentation remains, fundamentally, the same as that first used at Woods Hole in 1947 to measure directly the ion current crossing the squid axon membrane between a long axial electrode within the [redacted] and an external concentric electrode after a controlled change of potential difference across the membrane. A micropipette electrode has been used for measurement of the intra axonal potential and control of the membrane current to minimize the effect of internal and external electrolytic resistances, to simplify the axial electrode design construction and operation, and to improve stability of both the equipment and the axon.

Major Findings: The more important and numerous biological and physical factors which caused poor axon survival and unreliable data during the 1954 and 1955 seasons were reduced to tolerable levels and, in August and September, a considerable number of apparently satisfactory records were obtained.

Although no major results or final conclusions will be available until an accurate and efficient analytical routine has been developed and applied to the records, it is hoped that experiments on "normal" and deteriorating axons and the effects of variations of temperature, sodium, potassium, calcium and magnesium concentrations, and of ethyl alcohol and procaine will yield useful results.

From entirely superficial observation it seems probable that the present data are considerably better than any obtained since the inception of the line of investigation in 1947, -- the norm peak sodium permeabilities are several times larger, the sodium potentials are higher and the resting sodium inactivation is less, than previously reported. As preliminary and presently incidental items, it appears that "tris buffer" (trishydroxylmethyl amino methane) may be a more satisfactory material to displace sodium than is choline chloride, that the external magnesium ion may be a more important factor in the sodium permeability of this axon than is calcium, that the initiation of sodium ion movement may be more complicated than has been apparent before, and that it may be possible to move sodium ions electrically and quantitatively in or out across the axon membrane.

Significance to NINDB Research: The recently developed concept and the measurements of the sodium and potassium ion movements across the squid axon membrane offer a new, highly specific and general approach to the factors underlying normal and pathological nervous processes which cannot as yet be investigated directly in higher animals and man.

Proposed Course of Project: The extensive analyses of the records, as now planned and as far as practical, will proceed along the following lines:

1. The development of an accurate and efficient procedure for the separation of the ionic current caused by a sudden change of membrane potential difference into its components and the quantitative description of the sodium-on-and-off, and the potassium-on processes.

2. The careful characterization of the more active and stable axons to be used as the best available norm and the investigation of the nature of the process of the inevitable deterioration from that norm.

3. The dependence of the sodium and potassium permeabilities upon the external and internal concentrations of these ions.

4. The dependence of the various aspects of these permeabilities upon the temperature.

5. The dependence upon alterations of the external calcium and magnesium ion concentrations, particularly under those conditions for which the axon becomes spontaneously and repetitively active.

6. The dependence upon external ethyl alcohol and procaine concentrations, especially as impulse conduction becomes less certain and as it fails.

All of these factors are expected to have implications as to the nature of the underlying processes in squid and other nerves somewhat in proportion to the adequacy of the data and the power of the analyses, as well as the ability to project the information and concepts beyond experimental fact.

The axon cell, axial electrodes and their accessory equipment will be replaced or modified to improve their electrical characteristics and to minimize potential toxicities and the effects of injuries to the axon. The stability, reliability and speed of electronic control and recording equipment will be improved as much as possible. As further inadequacies of the 1956 procedures and data become apparent and when the living material is again available, the experimental program will be planned and executed.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-B-1
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$49,964	17,705	$67,669	2.96	.33	3.29

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2.66	.33	3.99	

13. BUDGET ACTIVITY:

RESEARCH

14. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-B-1
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

None

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Election of Kenneth S. Cole to membership in National Academy of Sciences and to Board of Trustees, Marine Biological Laboratory.

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-B-2
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Biophysics
LABORATORY

4. _____
SECTION

5. Bethesda, Md.
LOCATION

6. Ionic Permeabilities of Nerve Membranes -- Theoretical Investigations
PROJECT TITLE

7. Cole, K. S., FitzHugh, R.
PRINCIPAL INVESTIGATORS

8. Antosiewicz, H. A. (NBS), Franck, U. F.
OTHER INVESTIGATORS

9. None.

10. PROJECT DESCRIPTION:

Objectives: Investigate the bases, consequences and extensions of ionic permeability concepts and information by mathematical analysis and computation.

Methods Employed: Mathematical analysis by topological and other formal approaches and automatic numerical computation. Increasing reliance is being placed on electronic analog computation in this Laboratory while the more critical and extensive problems are investigated by digital computation at the National Bureau of Standards.

Major Findings: The SEAC computations of the propagated action potential of the Hodgkin-Huxley (H-H) mathematical model of the squid axon membrane have been continued. The value of the parameter upon which the conduction velocity depends has been found to the limit of accuracy of SEAC, and the early part of the curve, comprising the spike potential, has been obtained. The later part of the curve, representing the after potential, still diverges to infinity, and a further process of successive approximation is under way to obtain the complete action potential curve.

The requirements of an analog computer to solve the Hodgkin-Huxley equations have been investigated and commercial equipment ordered for this purpose. A program on the physiologically important properties of the H-H equations has been planned for this computer. In preparation for its use, considerable experience has been gained in the operation of the small Donner analog computer, which has been used to study such problems as the behavior of the linearized H-H equations near the resting state and the different types of threshold and oscillatory behavior obtainable from simple differential equations containing a cubic term.

It has been shown that the threshold behavior of the H-H equations can be understood as resulting from a saddle point in the phase plane of the reduced system containing only the variables V (membrane potential) and m (sodium activation), and that this saddle point disappears after a certain time as a result of the relatively slower changes in the variables n (potassium activation) and h (sodium inactivation). The presence of this temporary or "phantom" saddle point helps to explain the extreme sharpness of threshold found previously with SEAC.

Seen from the electrochemical and thermodynamical standpoint, the excitable nerve can be compared in its behavior with a number of non-biological "unstable dynamic systems," which are able to reproduce functionally almost the entire excitation physiology of excitable living tissues. Many "nerve models" of this kind have been proposed in order to yield better information about the physicochemical nature of excitation processes.

Some of these models, especially the well-known Ostwald-Lillie model have already been thoroughly investigated experimentally. Till now, however, no complete mathematical treatment of any of these model systems exists. This is being tried now for the case of the Ostwald-Lillie model. Such a treatment is desirable because it would allow a closer and a more useful comparison with the nerve and its mathematical description by the Hodgkin-Huxley differential equations.

It appears that the above-mentioned model is in some respects simpler to visualize than the nerve, because it seems to be possible to describe the model system only by three variables of state.

Analytical solutions for the transient and alternating current steady state electrical characteristics of a theoretical fixed charge membrane have been sought and not found in usable form even under quite simplified conditions. Qualitative support of intuitive generalizations has been found and digital numerical computations have been started.

Part A. Project Description Sheet (cont'd.) NINDB-B-2

Significance to NINDB Research: The increasing number of comparisons between the broad generalizations of electrophysiology and calculations based upon empirical differential equations of normal membrane ion movements are continuing to be so satisfactory as to encourage the assumption that these movements and the mechanisms by which they are controlled are a fundamental component of normal and pathological nervous processes.

Proposed Course of Project: When installed and operative, the analog computer will first be used to solve the Hodgkin-Huxley equations over a broad spectrum of physiologically important conditions. It will next be used to investigate possible modifications of these equations to extend their application to areas into which they are now inadequate. As new data become available, the value of alternative analytical forms and the physiological significance of the effects of experimental variables will receive increasing emphasis. Standards Eastern Automatic Computer should complete the propagating impulse calculation and a few minor tasks before it is retired. Preparations will be made to compute the far more difficult conditions for the initiation and blockade of a propagated impulse by the much more powerful anticipated successor to SEAC.

The topological investigations of threshold and cyclic systems will be continued. The analyses of the iron wire model and the fixed charge membrane should be brought to a logical halt.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-B-2
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$37,669	13,349	$51,018	2.31	—	2.31

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2.66	—	2.66	

13. BUDGET ACTIVITY:

RESEARCH

14. National Bureau of Standards
COOPERATING UNIT

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-B-2
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"The Nerve Trigger" by K. S. Cole, in "Physiological Triggers" published by American Physiological Society.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Kenneth S. Cole elected to membership in the National Academy of Sciences and to Board of Trustees, Marine Biological Laboratory.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-B-3
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Biophysics
LABORATORY

4. _____
SECTION

5. Bethesda, Md.
LOCATION

6. Correlation of Acetylcholinesterase inhibition spectrum with nerve action.
PROJECT TITLE

7. Moore, J. W.
PRINCIPAL INVESTIGATOR

8. Friess, S. L. (NMRI), Whitcomb, E. R.
OTHER INVESTIGATORS

9. None

10: PROJECT DESCRIPTION:

Objective: To determine the presence or absence of a correlation between the in vitro acetylcholinesterase inhibition spectrum of drugs and their blocking action on the propagated nerve action potential.

Methods Employed: A length of desheathed frog sciatic nerve is exposed to a conventional drug or one of a series of derivatives of ethylene diamine type compounds with selected geometries and electron distributions. The time course and extent of the depression of the A fiber action potential and the change of its conduction time are compared with the in vitro anticholinesterase activity of the agent.

Major Findings: No correlation has been found between the in vitro enzymatic inhibition and the depression or recovery of the action potential for a series of compounds when the inhibitory constant is varied by a factor of nearly a thousand fold. Prostigmine and other quarternary compounds, having a positive charge at all pH levels, failed to block impulse propagation. Similar concentrations of eserine and other tertiary compounds in which the positive charge decreases with increasing pH blocked impulses with greater effectiveness as the pH was increased.

Part A. Project Description Sheet (cont'd.) NINDB-B-3

The results of preliminary experiments on the action current at a single node suggest a basis for correlation with the whole nerve observations and promise a more useful experimental approach.

Significance to NINDB Research: These studies aid in evaluating the role of acetylcholinesterase in nerve functions and in characterizing the conditions for one type of nerve impulse blockade.

Proposed Course of Project: To follow the same screening process on the frog single node preparation where the effect of the drugs on the total ionic nodal current is available. When, as, and if the analysis of ionic currents components in the node becomes possible, this project will furnish a basis for and become a part of a more fundamental approach to the problems of ion permeability phenomena and mechanism.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-B-3
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,17	6,094	$23,290	.41	1.33	1.74

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.66	1.33	1.99	

13. BUDGET ACTIVITY:

RESEARCH

14. Naval Medical Research Institute
COOPERATING ORGANIZATIONS

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-B-4
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Biophysics
LABORATORY

4. _____
SECTION

5. Bethesda, Md.
LOCATION

6. Membrane Potentials of a Lobster Giant Axon.
PROJECT TITLE

7. Dalton, J. C.
PRINCIPAL INVESTIGATOR

8. _____
OTHER INVESTIGATORS

9. None

LO: PROJECT DESCRIPTION:

Objective: To test the possibilities of the lobster giant axon as a preparation to be used in general studies of ion permeabilities, to compare this axon with other nerve preparations which have already been investigated, and to use the preparation in studies of the actions of certain pharmacological agents with special reference to membrane oscillations and the production of repetitive activity.

Methods Employed: Resting potentials and spike potentials from the lobster giant axon are obtained by means of an intracellular microelectrode and recorded by conventional electrophysiological instruments. A circulation and cooling system permits changes in ionic composition and concentration, and the admission of drugs. Electrical stimulation of the nerve may be external or internal.

Major Findings: Any one of the three giant axons in the lobster circumoesophogeal commissures makes a rather simple, hardy preparation for the present investigations. It appears to have good possibilities for further experimentation on the types of ionic

problems which have been under investigation in this Laboratory. Its responses to high and low external potassium and to low external sodium are similar to the findings on other nerve preparations such as the squid giant axon. Low external calcium causes a fall in resting potential, reduction in spike amplitude, presence of spike undershoot, and may result in repetitive activity. The magnesium ion appears to be relatively unimportant, considerable increases or decreases in its external concentration causing little or no change. Changes in pH from 6.5 to 8.8 have no effect on the normal nerve. Both ethyl alcohol and acetone cause repetitive activity, a slow return of the spike potential to the baseline, and eventual reduction of resting potential and spike potential. The action of procaine is quite pH dependent and appears to be proportional to the amount of the free base form of the drug which exists at different pH values. Results of procaine treatment are increase in spike duration, and reduction in spike amplitude, with a decrease in resting potential at high drug concentration.

Significance to NINDB Research: These investigations are one aspect of the general problems of ionic permeabilities which are under investigation in this Laboratory, and, as such, are a mode of attack on the underlying questions of general nerve function. They are useful in providing additional evidence both of the common features and of the singularities of nerve phenomena. They have a deeper significance in that they present a possible transition between the ionic permeability analysis now only available for the exotic squid axon and the neurological problems of higher animals and man.

Proposed Course of Project: Further work on pharmacological agents, such as the so-called "stabilizers" and "unstabilizers" will be carried out, with special reference to the phenomenon of repetitive activity. As new techniques can be developed or present procedures miniaturized, the ionic currents in the lobster axon membrane will be determined -- to be tested as the common underlying basis of the conventional phenomena now being investigated.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-B-4
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$13,173	4,668	$17,841	1.08	.34	1.42

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1.34	.34	1.68	

13. BUDGET ACTIVITY:

RESEARCH

14. NONE
COOPERATING ORGANIZATIONS

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-B-5

2. NINDB
INSTITUTE

3. Biophysics
LABORATORY

4. _____
SECTION

5. Bethesda, Md.
LOCATION

6. Ionic Permeabilities of Nodal Membrane
PROJECT TITLE

7. Chang, J. J., Moore, J. W.
PRINCIPAL INVESTIGATORS

8. Cole, K. S.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: The measurement and the analysis of the ionic components of the membrane current in the single frog node to attempt an interpretation of the many phenomena characteristic of this most useful present representative of medullated nerve fibers.

Methods Employed: The electrical potential measurement and current control techniques and equipment as developed for the squid axon are modified to measure the ionic components in the single frog node using the double air gap preparation of Tasaki.

Major Findings: None.

Significance to NINDB Research: Medullated nerve fibers are such important components of neurological systems that it is not only interesting but practically important to know if -- and if so, to what extent -- the concepts and information now available only for the squid axon also apply to the nodal membrane.

Proposed Course of Project: Preliminary experiments with the present preparation and instrumentation will guide necessary further developments towards the stage at which it may become possible to describe the behavior of the ionic current components under the more important experimental conditions and to show that the known phenomena under these conditions are a necessary consequence of these current characteristics.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-B-5
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$15,198	5,386	$20,584	1.18	-	1.18

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1.68	-	1.68	

13. BUDGET ACTIVITY:

RESEARCH

14. None.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-1
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Development of Intrinsic Structures of the Human Brain.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR

8. None
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION

Objective: To conduct an embryological study of the genesis and subsequent development of nerve fiber tracts and groups of nerve cells in the human brain and spinal cord.

Methods employed: Study with the light microscope of serial sections of human embryos stained by certain neurological silver methods to bring out the fine details of neuron growth. A collection of human embryos which has been assembled gradually over the last 20 years constitutes the material for the present study.

Major findings: Further observations have been made on the organization of the primary motor neuron groups in the brain stem of embryos during the fourth to the seventh weeks of gestation. Development of certain secondary tracts such as the medial longitudinal fasciculus and the funiculae of the spinal cord has

Part A. Project Description (cont'd.)

NINDB-NA-1
SERIAL NUMBER

been studied. One of the principal observations is that the first longitudinal pathways to be laid down in early embryolic life (by the 6th week) come to occupy the most internal positions in the adult brain stem. Those which are laid down later (after the 7th week) come to occupy an intermediate position and those which are most recently formed occupy the most peripheral positions in the adult brain stem. Therefore, in looking at a cross-section through the adult human brain stem, one can read sequential ontogeny of its fiber tracts.

Significance: Knowledge of intrinsic development of the human brain is scanty; there has been no systematic study. Most descriptions of brain development have been based on material which was not stained specifically for nervous structures. Until we have detailed knowledge of the intrinsic structural development of the human brain, we will not have adequate basis for understanding such things as the normal process of aging, the advent of pathological conditions and the significance of functional aberrations.

Proposed course of the project: To continue these studies, which are of such nature that progress is made slowly and gradually, and to accumulate information and make it available by publication.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-1
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,903	3,867	$14,770	.20	1.10	1.30

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	1.10	1.30	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-1

16. PUBLICATIONS:

Windle, W. F. discussing "The Ultrastructure of Synapses in Relation to Certain Cytoplasmic Double Membranes" by Dr. J. David Robertson. Symp. Neurochem., Chicago, (in press)

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB-NA-2
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and regeneration
SECTION

5. Bethesda

6. Regeneration in the Central Nervous System
PROJECT TITLE

7. W. F. Windle, John O. Smart, Jane Joralemon, Elizabeth Dorrill,
PRINCIPAL INVESTIGATOR

8. R. L. Sidman
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To study the factors regulating regeneration in the central nervous system. To learn the role played by the neuroglia cells in degeneration and regeneration. To attempt to alter the normal response of the central nervous system to injury in such a way that a milieu favorable to regeneration will develop. To learn why regeneration occurs so readily in the central nervous system of the lower vertebrates and is so difficult to achieve in mammals and man.

Methods employed: (a) Spinal cord transection in various species of mammals followed by institution of various

Part A. Project Description (Cont'd.)

NINDB-NA-2
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types of therapy to try to alter the normal response of the spinal cord to injury.

(b) Production of lesions in other parts of the central nervous system, especially the cerebal hemispheres, and following the course of degeneration and regeneration in relation to age.

(c) Production of central nervous lesions in mammals during different states of metabolism, especially during hibernation.

(d) Study of material by means of neurohistological and histochemical techniques.

Major findings: No major findings can be added to those of last report. Histological study of a large mass of material is under way. Additional operations have been delayed until a thorough study has been made of accumulated material. Methods of attacking the question of role of neuroglia cells have been under study. A conference on the subject of "The Biology of Neuroglia" was held at Bethesda and a monograph on the subject is being prepared for publication. A final report of the histological studies on regeneration in the spinal cord will be made when all data are tabulated.

The study of relation of age to regeneration across stab wounds in brains of kittens is progressing slowly; we are awaiting work-up of a large mass of histological material.

Significance: Importance of studying the phenomenum of regeneration in the central nervous system is self evident. Results of this study may be applicable to almost any traumatic injury of the brain or spinal cord and may throw light on any one of a number of degenerative diseases.

Proposed course of project: It is planned to extend the study to other species of animals and to utilize other therapeutic agents in an effort to enhance the regeneration after cord section in cats and other animals. Hybernating animals will be used in an effort to compare effects of spinal cord transection during hypothermia and hybernation with those in the active state.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-2
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$15,765	5,592	$21,357	.53	1.47	[redacted]00

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.53	1.14	1.67	

13. BUDGET ACTIVITY: RESEARCH

14. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-2
SERIAL NUMBER

16. PUBLICATIONS:

Windle, W. F., Editor, "Regeneration in the Central Nervous System", xx+311 pp.; Springfield, Ill., Charles C. Thomas, 1955.

Windle, W. F., Jae L. Littrell, J. O. Smart and Jane Joralemon. "Regeneration in the Cord of Spinal Monkeys". Neurology, 6: 420-428, 1956.

Windle, W. F., "Regeneration of Axons in the Vertebrate Central Nervous System". Physiol. Rev., (in press).

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-3
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration

5. Bethesda

6. Regeneration in the Peripheral Nervous System
PROJECT TITLE

7. Lloyd Guth
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATOR(S)

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine the extent to which the functional and morphological specificities of mammalian nerves are fixed and the extent to which they may be altered.

Methods employed: Cross-anastomosis of different nerves using the arterial sleeve suture technique was employed to secure heterogeneous nerve regeneration. The following operations (with appropriate controls) have been performed in the cat and rat: Proximal vagus to distal cervical sympathetic trunk; proximal hypoglossal to distal glossopharyngeal; proximal vagus to distal glossopharyngeal.

Part A. Project Description (cont'd.) NINDB-NA-3
SERIAL NUMBER

Major findings: The morphological and physiological results of heterogeneous nerve regeneration have been studied. (1) Following vago-sympathetic anastomosis ear temperature function was shown to return to normal. This functional restitution is dependent upon the integrity of the "foreign" vagus nerve, and is not a passive phenomenon but is mediated by active alterations in blood flow through the ear.

(2) Transection of the glossopharyngeal nerve results in disappearance of all taste buds on the circumvallate papilla with replacement by stratified squamous epithelium. It is also accompanied by epithelial atrophy even in regions of the papilla devoid of taste buds. Reinnervation of the papilla by glossopharyngeal or vagal fibers results in redifferentiation of the taste buds. Reinnervation by hypoglossal fibers appears to result only in a temporary reappearance of taste buds.

Significance: (1) If the restored ear temperature regulatory reflexes can be proved to be mediated neurally this will be the first demonstration of alteration of neuronal specificity in the mammal. If an extra-neural control over ear temperature regulatory function is demonstrated this will show that the cutaneous vasomotor reflexes mediating temperature regulation may operate without active neural participation.

(2) The trophic relationship between nerve and epithelium and nerve and taste buds is one of the few well-documented trophic nerve effects in the adult mammal. The chemical factors in the nerve mediating this relationship are not known, but their absence in motor nerves is significant.

Proposed course of project: (1) In the normal cat as well as in the cat having a vagally reinnervated sympathetic pathway, stimulation experiments will be performed to study the mechanism underlying the temperature-regulatory reflexes.

(2) Further studies will be performed to elucidate whether relationship between nerve and taste bud and epithelium is truly a trophic one or whether other explanations (e.g. vascular) for the observed results are

Part A. Project Description (cont'd.)

NINDB-NA-3
SERIAL NUMBER

plausible.

(3) The project on rate of nerve regeneration has been discontinued because of inadequacy of available techniques.

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Part B: Budget Data

11. NINDB-NA-3
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$17,085	6,060	$23,145	1.00	.80	1.80

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	1.00	.80	1.80	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-3
SERIAL NUMBER

16. PUBLICATIONS:

Guth, L., Functional recovery following vago-sympathetic anastomosis in the cat. Am.J.Physiol. 185:205, 1956.

Guth, L., Regeneration in the mammalian peripheral nervous system. Physiol.Rev., Oct.1956 (in press)

17. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-4
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration

5. Bethesda

6. Process of Aging in the Central Nervous System
PROJECT TITLE

7. Harry H. Wilcox,
PRINCIPAL INVESTIGATOR

8. W. F. Windle, Jane Joralemon
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To study the normal development of the nervous system, especially the brain, from early embryonic life to extreme old age in order to try to understand the process of aging as it occurs normally in the brain unaffected by degenerative diseases.

Methods employed: There are three aspects of this project. (a) One, reported in Project: NA-1, is the study of early stages in development of the human brain. (b) The methods employed for the second part are: qualitative visual study with the light microscope, quantitative enumeration of nerve cells and neuroglia cells, and measurements of these elements in brains of healthy guinea pigs from early life to extreme old age. (c) The third part of the study involves evaluation of the effects of producing lesions in the brains of cats at birth and at various ages after birth to determine

Part A. Project Description (cont'd.)

whether or not the factor of age enters into the processes of regeneration and repair. This part of the study will constitute report in the project: Regeneration in the Central Nervous System. (NINDB-NA-2)

Major findings: Part (b) of this project is being carried out in the Department of Anatomy, University of Tennessee, Memphis, under contract in cooperation with the Laboratory of Neuroanatomical Sciences, NINDB. The principal investigator has assembled a series of specimens from a single colony of guinea pigs which has been maintained under closely controlled conditions for many years. The series ranges from 78 days to 2,765 days of age. Animals were sacrificed under controlled conditions by the perfusion-fixation technique. All were prepared by the same histological staining methods and are being studied qualitatively and quantitatively.

The most striking change that accompanies aging in the brain of the healthy guinea pig is accumulation of pigment in the cytoplasm of nerve cells. Different groups of nerve cells accumulate it at different rates. The pigment does not replace other components of the cytoplasm, insofar as can be determined, but is added in such a way that the size of the neuron gradually increases slightly with aging. The investigator has failed to confirm the often described changes, such as "chronic ganglian cell disease", "neuron aphagia", etc., and has demonstrated that some of these "changes" are postmortem and fixation artifacts, both of which were eliminated from the present study. Contrary to the reports of some other investigators, the present research has failed to demonstrate loss of nerve cells in the cortex of the cerebellum with aging. The brain vasculature appears to be more changed in old animals' brains than the neurons themselves.

Significance: This is the first thorough study of any one species in which factors of fixation and histological preparation have been accurately controlled. It is the first one in which all questions of immersion fixation artifacts, postmortem artifacts and the complication of disease processes have been eliminated. It has shown that marked changes in brains with aging must be sought in some

Part A. Project Description (cont'd.)

elements other than nerve cells.

Proposed course of project: The project is under contract with the University of Tennessee and has been extended. Plans are under way to enlarge the staff of personnel working on the problem, to extend the work to another species, and to seek evidence of changes in neuroglia.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-4
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,153	3,596	$13,749	.20	1.00	1.20

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	1.13	1.33	

13. BUDGET ACTIVITY: RESEARCH

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-4
SERIAL NUMBER

16. PUBLICATIONS:

Wilcox, H. H., 1956. Present Status of our Knowledge of Aging in the Nervous System. (In press. To be published as a chapter of a monograph based on the transactions of the 9th Annual Michigan Conference on Aging).

Windle, W. F., 1956. Discussion of paper by Warren Andrew entitled "Structural Alterations in the Nervous System with Aging" (In press. Research Publication Association for Research in Nervous and Mental Diseases).

Wilcox, H. H. 1955. Aging Effects on Cranial Nerve Nuclei in Guinea Pigs. Anatomical Record, Vol. 121:381.

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-5
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Study of the influence of nerves upon their end organs.
PROJECT TITLE

7. Richard L. Sidman
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To explore the "trophic" function of nerves -- the means other than impulse conduction by which nerves may influence the structure and function of their end organs.

Methods: Two major experimental methods are being set up. (1) Tissue culture laboratory. Fragments of various mammalian (including human) organs can differentiate and maintain intact normal structure in vitro. The interaction of two organs, e.g., nerve and adipose tissue, can be analyzed. Also the direct effect of chemicals, such as hormones or neurohumors, upon an end organ can be studied. (2) Cold-blooded vertebrate laboratory. Adult newts regenerate an

Part A. Project Description (cont'd)

amputated limb, and this growth process is controlled by the peripheral nervous system as a trophic function. Its mechanism can be analyzed by perfusing small volumes of chemical substances continuously into the limb in a manner which may be analogous to the release of regeneration-stimulating factors by the nerve.

Major Findings: There are none to report as the laboratories are being organized.

Significance: The significance of the trophic function of nerves will become clearer if its existence can be demonstrated for a wider range of end organs and if its mechanism is clarified. An understanding of almost any new physiological function leads in time to a further understanding and control of disease.

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Part B: Budget Data

11. NINDB-NA-5
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,777	1	6.1	.2	.1	.30

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.2			

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NA-5
SERIAL NUMBER

16. PUBLICATIONS:

Sidman, R. L. Histogenesis of brown adipose tissue in vivo and in organ culture. Anat. Rec., 1956, 124:581-602.

Sidman, R. L. The direct effect of insulin on organ cultures of brown fat. Anat. Rec., 1956, 124:723-740.

Singer, H., D. Flinker and R. L. Sidman. Nerve destruction by colchicine resulting in suppression of limb regeneration in adult Triturus. J. Exp. Zool., 1956, 131:267-300.

17. NONE

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-6
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Study of the structure and chemistry of vertebrate photoreceptor cells.
PROJECT TITLE

7. Richard L. Sidman
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To correlate the chemical aspects of vision with the complex structure of rod and cone photoreceptor cells, and particularly to measure the absorption spectra of rhodopsin in intact rod outer segments.

Methods: This study uses the new optical methods of refractometry and interference microscopy, which allow an unparalleled examination of the structure of teased living photoreceptor cells and also yield quantitative data on the refractive indices and concentrations of solids and water in the various segments of rod and cone cells. When living rod cells are mounted in an albumin medium matching the cells in refractive index an optically clear suspension is obtained, and the absorption spectrum of intracellular rhodopsin can be measured directly in a spectrophotometer.

Part A. Project Description (cont'd)

Major Findings: This project is too new to report new findings.

Significance: The chemistry of vision is better understood than the chemistry of any other sensory system. However, less is known of how the chemical reactions relate to the special structure of photoreceptor cells. The investigation should increase our understanding on how sensory information is received by the primary sensory elements of the retina.

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Part B: Budget Data

11. NINDB-NA-6
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,719	1,673	$6,392	.33	.17	.50

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.17	.50	

13. BUDGET ACTIVITY: RESEARCH

14. None

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Part C: Honors, Awards & Publications

15. NINDB-NA-6
SERIAL NUMBER

16. PUBLICATIONS:

Barer, R. and R. L. Sidman The absorption spectrum of rhodopsin in solution and in intact rods. J. Physiol., 1955, 129:60-61 P.

Sidman, R. L. The structure and concentration of solids in photoreceptor cells studied by refractometry and interference microscopy. J. Biophys. Biochem. Cytol., 1957, 3: in press.

17. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-7
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Induction of hypokinesia, tremor, rigidity and related phenomena in laboratory animals by means of reserpine and other drugs.
PROJECT TITLE

7. W. F. Windle
PRINCIPAL INVESTIGATOR

8. Jan Cammermeyer, Paul Glees, Jane Joralemon, Earl Feringa, John O. Smart
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION

Objectives: Further exploration of phenomena in animals which resemble paralysis agitans in human beings by induction with drugs, especially reserpine.

Exploration of anatomical correlates of these phenomena.

Exploration of means of alleviating the phenomena by surgical and medical therapy.

Part A. Project Description (cont'd.)

Methods employed: Work during the past year has been confined to two species of monkeys (Macaca mulatta and Macaca Cerepithecus), the cat and the chimpanzee. Most work has been carried out with reserpine although chlorpromazine and promazine have been used to some extent. Observations of the animals under various doses of these drugs have been carried out, emphasizing tremor, rigidity and hypokinesia. Experiments have been recorded in 2D and 3D motion pictures. Anatomical material has been collected for neurohistological studies.

Major findings: 1. Short term effects of high doses of reserpine.

(a) Monkeys. Single doses of reserpine given orally, intravenously or intermuscularly, 2.5 - 5 mg per kg, resulted in appearance of a group of phenomena consisting of muscular rigidity (of the cogwheel type); hypokinesia, lethargy, torpor and catalepsy; tremor at rest (varying inversely with the degree of lethargy); sialorrhea; and other phenomena which are somewhat like those in human patients with Parkinsonism. The phenomena were transient, the animals apparently recovering completely in 48 to 72 hours.

(b) Cats. Single or multiple doses of reserpine, 2.5 - 5 mg per kg, were followed by prolonged effects. The animals became lethargic and were markedly cataleptic; they exhibited tremors; had increased rigidity; and showed a number of visceral symptoms of which pupillary constriction and diarrhea were the most marked. The animals did not recover from these effects in 48 to 72 hours, as did the monkeys. Even after 2 weeks there was little change in many of the animals' appearance. One that has been under observation for three months is not yet normal; it remains lethargic and retains marked pupillary constriction. Histopathological studies of the brains of cats given reserpine are in progress. At general postmortem some of these animals exhibited subserosal and submucosal hemorrhages and, in two instances, apparently had peptic ulcers which have not yet been verified histologically. Many died.

2. Long term effects of low dosage.

(a) Two African green monkeys have been maintained

Part A. Project Description (cont'd.)

on reserpine, 0.2 - 0.6 mg/kg, for 13 months. These animals have been given the drug each morning, 7 days per week, with only occasional interruption to determine persistence of the effect. They have attained a state in which marked and violent resting tremors occur almost continually, exacerbating cyclically 3-5 hours after administration of each daily dose. As yet no permanent effects have been observed upon withdrawal of the drug.

(b) Reserpine in doses of 0.2 - 0.4 mg/kg have been given to 2 chimpanzees, daily over periods of 2-4 weeks. This has elicited bizarre behavioral reactions in which tremor, rigidity, lethargy, akinesia and the other phenomena have been observed. Curious spasmodic twitches and muscle contractures occurred.

(c) Four rhesus monkeys, Macaca mulatta, have been rendered chronically tremorous by daily administration of reserpine in doses of 0.2 - 0.6 mg/kg. A very small bore catheter was then inserted into the brain in the region of the globus pallidus with the Horsley-Clarke instrument. Injection of a solution of procaine hydrocloride resulted in modification or abolition of the reserpine effect, i.e., the tremor and rigidity were reduced contralaterally when the catheter had reached the predicted location of the globus pallidus and ansa lenticularis. This effect was transient. Subsequently, absolute alcohol was injected and the lesion thus produced at the end of the catheter resulted in similar modification of the tremor and rigidity without any detectable loss of strength or voluntary movement in two instances.

Significance: A reliable method for producing tremor and rigidity in monkeys has been developed. It has been demonstrated that this technique can be used as a tool to study alleviation of these phenomena. We hope to learn whether or not development of the reserpine symptoms requires the same pathways and centers as human Parkinsonism. If they do, we may have acceptable animal in which to test anti-Parkinsonism drugs or anti-Parkinsonism surgical procedures. The degeneration after the surgical lesion may give clues to the paths involved in Parkinsonism.

Part A. Project Description (cont'd.)

The prolonged effects of even a single moderately high dose of reserpine and the appearance of vascular lesions in the viscera of cats requires further study and raises doubts that the drug has only transient effects in other species.

Proposed course of project: It is planned to complete the physiological experiments now in progress, to prepare motion picture films illustrating them, to extend the histopathological aspects of the work and to report findings.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-7
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57						

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57				

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NA-7
SERIAL NUMBER

16. PUBLICATIONS:

Windle, W. F., J. Cammermeyer, J. Joralemon, J. O. Smart, E. R. Feringa and M. P. McQuillen (1956). Effects of Reserpine in Animals, Especially Primates. Trans. Am. Neur. Assoc. (in press).

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-8
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Stomach factors in hunger and drive discrimination.
PROJECT TITLE

7. C. J. Bailey
PRINCIPAL INVESTIGATOR(S)

8. Roberta Ashburner, John O. Smart
OTHER INVESTIGATORS

9. PROJECT DESCRIPTION:

Objectives: To investigate the role of stomach innervation in hunger when it is functioning as a drive or as a cue during learning and in the original learning of hunger itself.

Methods employed: (a) Surgical denervation of the stomach before and after radical changes in food consumption. Two such changes are: the first experience of eating and the great increase in food consumption resulting from destruction of the ventromedial nucleus. (b) Training of animals to discriminate the cues of hunger and thirst on the basis of a third drive; testing by varying the fullness of the stomach (and hence the cues arising from the stomach) independently of the need for food or water.

Part A. Project Description (cont'd.)

Major findings: (a) Techniques for electrolytic destruction of the ventromedial nucleus in rats have been investigated previously. Stomach denervation was tried in adult rats and guinea pigs and in newborn guinea pigs. (b) In previous experiments, a hunger-thirst discrimination using a third drive was established and variations in stomach distension have been tested in such discriminations using food and water as rewards. The training of a group of rats in a hunger-thirst discrimination reinforced by rewarding a third drive (a difficult task for the rat) in order to test variations in stomach distension was recently begun, but time was not available to train the rats consistently enough or long enough to complete their education.

Significance: Experiments involving denervation of the stomach should provide information relevant to a clearer understanding of the mechanisms involved in hunger and should determine the importance of cues from the stomach in the learning of hunger. The experiment involving drive-discrimination utilization should shed light upon a theoretical controversy concerning the function of drives, particularly the hunger drive, in learning.

Proposed course of project: The future of this project will depend on decisions in respect to development of facilities in San Juan for its continuation.

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Part B: Budget Data

11. NINDB-NA-8
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	2,941	1,039	3,980	—	.50	.50

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	—	.60	.60	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB NA-9
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Effects of anoxia at birth on brain structure and function.
PROJECT TITLE

7. C. J. Bailey, Marisa I.R. Ramirez de Arellano and W. F. Windle
PRINCIPAL INVESTIGATORS

8. Roberta Ashburner, Doris Curran, John Comerford and Samuel E. Long
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To learn whether anoxia or asphyxia induced at, before or immediately after birth, i.e., in the late perinatal period can lead to neurological and psychological deficits after birth. To study the nature of these deficits.

Methods employed: Experimental surgical approach in pregnant guinea pigs to asphyxiate the young. The resuscitation in newborn followed by (a) observation on neuromuscular and neurosensory behavior, (b) observation of the effects on the electro-encephalogram, (c) use of a simple alternation maze for determining impairment of ability to learn, and (d) studies of the brains and other organs of these animals by histological methods. Non-asphyxiated littermate controls will be used throughout.

Part A. Project Description (cont'd.)

Major findings: Late fetal and newborn guinea pigs have been asphyxiated, resuscitated and observed for alteration in behavior and for impairment of ability to learn simple maze problems. (a) There appears to be some correlation between the amount of asphyxia and severity of neuromuscular damage after resuscitation. This correlation is more exact than was encountered in earlier experiments by Windle, Becker and others. (b) A feasible technique for application of scalp electrodes without anesthesia has been worked out. Technically acceptable EEG recordings have been obtained on 53 animals. Data have not been analyzed. (c) The degree of asphyxiation in most of the experiments was somewhat less than in earlier studies. The experiments using the alternation maze have provided a large mass of data which have not been analyzed. Material is being collected for histopathological studies of the nervous system, but as yet is too incomplete to report findings.

Significance: Present study helps form the basis for understanding certain neurological and psychological deficits in the human being which may result from adverse factors in the perinatal period. It has direct bearing on the cause and prevention of cerebral palsy, mental retardation, certain types of epilepsy, deafness and blindness.

Proposed course of project: This project will become an integral part of the cooperative research project in San Juan. It is basic to experiments that are being planned in primates and will particularly be carried out by some of the personnel who are engaging in the primate studies in San Juan.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB NA-9
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$23,117	8,190	$31,307	.80	1.80	2.60

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.70	1.90	2.60	

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB NA-9
SERIAL NUMBER

16. PUBLICATIONS:

Windle, W. F. (1956) "Asphyxia Neonatorum, Experiments in the Guinea Pig." being a preface to a collection of reprinted articles on the subject. U.S. Dept. H.E.W., 1956.

Windle, W. F., Editor. "Asphyxia Neonatorum, Brain Damage and Impairment of Learning" (in manuscript, 1956)

17. NONE

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-10
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. Ultrastructure of nervous system.
PROJECT TITLE

7. Sanford L. Palay
PRINCIPAL INVESTIGATOR

8. Milton W. Brightman, S. M. McGee-Russell, Miss Catherine Crigler
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To study the ultrastructure of nervous tissue, particularly the synapse and the glia with special attention to the correlation between structure and function.

Methods employed: The principal instrument employed will be the electron microscope.

Major findings: Dr. Palay arrived at NIH on

Part A. Project Description (cont'd.)

July 1, 1956. Dr. Russell arrived at NIH on September 1, 1956, but because of delays in completion of the construction and the installation of equipment for this section, the project has not yet been initiated.

Significance: Electron microscopy has already revealed the ultrastructure of the synapse in some detail. The meaning of this structure in terms of function now awaits discovery. Some neurophysiologists are already speculating that the small synaptic vesicles within the terminals contain acetylcholine, but no evidence has yet been adduced. It is important for an understanding of the mechanisms of impulse transmission to have functional correlates for the ultrastructure revealed by electron microscopy.

Studies on the morphology and function of glia are being stimulated by the International Conference held at Stone House last March. A thorough study of the morphology of these mysterious cells will help to elucidate their function and their role in nutrition, support, and activity of the nervous system.

Proposed course of project: This project cannot be activated until the promised facilities are available.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-10
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$3.6[illegible]	11,580	141,240	1.82	1.14	2.96

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
1.00	1.20	2.20	

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-1[illegible]
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. Quantitative histochemical methods.
PROJECT TITLE

7. R. W. Albers
PRINCIPAL INVESTIGATOR

8. M. W. Brightman, R. O. Brady
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To extend the range of application of quantitative histochemistry.

Methods employed: Standard methods of biological, biochemical and radiochemical measurements are modified for use in the analysis of microgram and sub-microgram samples of tissue from the nervous system.

Major findings: (1) A new and simplified technique

Part A. Project Description (cont'd.)

for the measurement of cholinesterases has been developed. (2) A simple and direct method for measuring the content of neurosecretory material in sub-microgram samples of the neurohypophysial system is now under study in collaboration with Dr. Brightman. (3) Preliminary experiments carried out in collaboration with Dr. Brady have demonstrated the feasibility of determining decarboxylase activity on microgram tissue samples utilizing the appropriate C-14 labelled substrates.

Significance: As these methods are perfected they are applied to quantitative histochemical studies of the nervous system.

Proposed course of project: (1) The cholinesterase method is at present in manuscript. Further developmental work is not contemplated. (2) Further studies to test the validity and usefulness of the neurosecretory assay are planned. (3) The radio-chemical technique will be applied to decarboxylase systems of apparent importance to the biochemistry of the nervous system. To some extent the course of these studies will be governed by the availability of the C-14 labelled substrates.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-11
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$1,[illegible]	2[illegible]	$1,700	.25	1.00	1.25

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.25	1.25	1.50	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-12
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. Quantitative histochemical studies of the nervous system.
PROJECT TITLE

7. R. W. Albers
PRINCIPAL INVESTIGATOR

8. M. W. Brightman
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To explore the chemical organization of the nervous system at the histological and the cytological level.

Methods employed: The principal methods are based upon those of Linderstrøm-Lang and of Lowry, which employ frozen-dried tissue sections for obtaining samples of relatively homogeneous cytological composition. Enzymatic activities and biochemical composition are but slightly altered from that of fresh tissue in most instances. Samples having a dry weight of .01-50[illegible]. may be subjected to a wide variety of analyses.

Major findings: (1) Through a comparative study of normal and atrophic magnocellular laminae of the lateral geniculate body, it is possible to deduce the enzymatic activities of the glial component of this area. The enzymatic contribution of the glia has been found to be a significant fraction of the total in the cases studied, and is different for different enzymes. (2) We have found that a protein fraction can be extracted from the posterior pituitary gland of the rat which is characteristic of this tissue. The amount of this material is greatly reduced in the chronically dehydrated animal, and hence is probably related to, if not identical with, the neurosecretory product.

Significance: This area of research is basic to an understanding of the interaction of the cytological elements of the nervous system at the biochemical level.

Proposed course of project: (1) The number of enzyme systems studied with respect to the enzymatic activity of neuroglia will be extended as new methods are developed. (2) The neurohypophysial secretory system will be studied with respect to its response to various physiological stimuli. (3) The general histochemical distribution of several decarboxylases will be explored in the nervous system.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-12
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$3,891	1 6	$4 5 97	.25	.25	.50

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.5	.2	5	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-12
SERIAL NUMBER

16. PUBLICATIONS:

Albers, R. W., (1956) Comparative Biochemistry of the Normal and Atrophic Lateral Geniculate. J. Histochem. Cytochem. (in press).

17. None

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Calendar Year 1956

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-13
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. Cholinesterase activity of mammalian neurosecretory system.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR

8. R. W. Albers
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine changes in enzyme activity of supraoptic and paraventricular nuclei at rest and during secretory activity.

Methods: (1) Koelle histochemical method for cholinesterase (2) A new microquantitative method for cholinesterase.

Major findings: (1) Both nuclei have true cholinesterase. The pars nervosa does not show activity.

Significance: Responses of the neurosecretory system to different stimuli may be followed on a qualitative and quantitative basis.

Part A. Project Description (cont'd.)

Proposed course of project: Completion of this study and application of these techniques to related problems of neurosecretion.

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Part B: Budget Data

11. NINDB-NA-13
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$5,432	1,923	$7,355	.45	.30	.75

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.45	.30	.75	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-14
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. The effect of the circulating titre of autidiuretic hormone on the release of this hormone from the neurohypophysis.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR

8. R. W. Albers
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine whether circulating levels of posterior lobe hormones exert an effect on the output of these hormones and of neurosecretory material from the rat neurohypophysis.

Methods: (1) The development of a sensitive bioassay technique for antidiuretic hormone utilizing urine flow measurements. (2) Extractions of the pars nervosa with different solvents.

Major findings: (1) Our bioassay is sensitive and a number of tests may be made on a single animal. (2) Extractions have yielded a protein substance, the quantity of which varies with the physiological

Part A. Project Description (cont'd.)

state of the rat. (3) Histological study indicates no correlation of stainable material in the neurohypophysis with exogenous hormone injected intramuscularly.

Significance: Hormone injected intramuscularly does not affect the depletion of neurosecretory material from the neurohypophysis of the dehydrated rat. A continous, intravascular infusion, found to be feasible, may be effective.

Proposed course of project: Continuous infusion of hormone into the blood of dehydrated rats and the testing of effects, histologically and with the two methods listed above, will be performed.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-14
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$5,281	$1871	$7,152	.45	.30	.75

FY '57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.45	.30	.75	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-15
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. Relationship between neurosecretion and milk ejection.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine whether or not a depletion of neurosecretory material occurs concomitantly with release of hormones from neurohypophysis in response to various stimuli.

Methods: Mice were allowed to nurse their young for various periods of time under different circumstances. The brains of these mice were stained by special methods. The amount of neurosecretory material was correlated with the period of suckling.

Major findings: The stimuli of suckling and of behavior associated with suckling resulted in a depletion of neurosecretory material from the hypothalamo-hypophysial system.

Part A. Project Description (cont'd,)

Significance: These experiments indicate a close relationship between the central nervous system and the endocrine system involving the pathway linking hypothalamus and neurohypophysis.

Proposed course of project: This project has been completed and will be prepared for publication.

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Part B: Budget Data

11. NINDB-NA-15
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
#5,307	1923	†7,230	.20	.80	1.00

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.20	.80	1.00	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-16
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. Vascular supply of the spinal cord.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine the extrinsic and intrinsic vascular supply of the spinal cord of the cat.

Methods: A simplified india-ink-gelatin-formalin perfusion technique has been used to inject the entire vascular bed.

Differentiation between arteries and veins was made with two methods: (a) gelatin-corn-starch medium developed with iodine. (b) cinnabar injection following the introduction of india-ink-gelatin.

Major findings: (1) There is a free anastomosis between dorsal

Part A. Project Description (cont'd.)

and neutral trunks. (2) No great radicular artery is present, but a large radicular vein, which drains the lumbo-sacral segment, is a consistent finding. (3) The comparatively highly vascular dura mater is in striking contrast to that of other species, excepting the shrew.

Significance: The radicular vessels with their ascending and descending tributaries, and the extensive venous drainage of the dura are important anatomical factors to be considered in any experimental manipulation of the cord.

Proposed course of project: Measurements of the intrinsic vasculature of different segments are being completed, and the work is being prepared for publication. The study on the other species will be concluded pending the collection of more shrew material.

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Part B: Budget Data

11. NINDB-NA-16
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$4,862	1,725	$6,587	.30	.35	.75

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.20	.30	.50	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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Part C: Honors, Awards & Publications

15. NINDB-NA-16
SERIAL NUMBER

16. PUBLICATIONS:

Brightman, Milton W. Comparative Anatomy of Spinal Cord Vasculature. Anat. Rec. 124: P. 264, 1956

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-17
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Neurocytology
SECTION

5. Bethesda

6. X-Irradiation of the hypothalamus.
PROJECT TITLE

7. Milton W. Brightman
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: (1) A new method of producing selective lesions of the supraoptic and paraventricular nuclei of the hypothalamus. (2) To determine whether increased metabolic activity of neuroendocrine cells enhance their susceptibility to X-irradiation.

Methods: The diencephalon of hydrated and dehydrated rats was exposed to high dosages of X-rays. The leucocyte count, water intake and urine output were followed for various periods after the irradiation. The brains were examined with a variety of techniques.

Major findings: (1) The neurosecretory nuclei do not appear to be more susceptible to irradiation injury than adjacent nuclei. (2) The state of hydration has no apparent effect on response of brain

Part A. Project Description (cont'd.)

cells to irradiation. (3) The earliest changes are vascular. Structures immediately adjacent to petechial hemorrhages are relatively intact.

Significance: Stimulation of these neuroendocrine cells does not enhance their susceptibility to irradiation damage. A differential response to X-irradiation occurs in the central nervous system.

Proposed course of project: Completion of the project.

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Part B: Budget Data

11. NINDB-NA-17
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	$7,500	2,661	$10,161	.20	.80	1.00

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY '57	.20	.80	1.00	—

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-18
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Experimental Neuropathology
SECTION

5. Bethesda

6. Pathogenetical Factors in the Development of Myelopathies
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR

8. Helen Ramsey
OTHER INVESTIGATOR(S)

9. None

10. PROJECT DESCRIPTION:

Objectives: (a) To obtain information about the histological and physical qualities of the spinal cord which are significant to maintain tissue tension and proper blood circulation. (b) To determine the extent of abnormality in histological and physical qualities necessary to interfere with spinal cord function.

Methods employed: The measurement of volume of

Part A. Project Description (cont'd.)

spinal cord segments and regions in cat, dog and monkey.

Apply conventional histological techniques and special ones as microincineration, histochemical procedures and semicolloidal dyes for vascular permeability. To measure the size of cells.

Major findings: (a) The normal proportion of spinal cord is expressed by an index which varies with species and the size of the animals.

(b) The swelling tendency of the spinal cord as demonstrated by submerging the spinal cord in distilled water is different for species and regions, also the region showing maximum of response varies with species and the maximum of reaction depends on the weight of the animal.

(c) The effect of fixatives is influenced by temperature, concentration admixture of salt, and duration of fixation. With isotonic fixatives the volume of spinal cord regions retains normal proportion and "index" whereas with hypotonic solutions the "index" is altered and the regions exhibit swelling which is greatest for the thoracic regions in cats. The maasurement of nuclear size disclosed that the nuclei were influenced by the concentration and composition of fixatives used, and the influence varied with regions and size of animals.

(d) The effect of narcosis on the spinal cord volume was studied in monkey and dogs and showed changes which varied with weight of animals, duration of narcosis and regions of spinal cord.

(e) Dog material shows in unusually high percentage, both meningoencephalitis and severe hydrocephalus.

Significance: These studies have demonstrated labile physical qualities inherent of the spinal cord which may play an important role for maintenance of spinal cord function. Further studies of the factors involved may prove

Part A. Project Description (cont'd.)

helpful to understand the mechanism of transient symptoms, ascending and descending symptomsatology, the frequent complication of the spinal cord to other diseases as concussion eclampsia, the severe changes superimposed on such conditions as demyelinating and viral myelopathies the insidious formation of gliosis and cavities through the spinal cord, etc.

The study of dog brain material shows that this species is useful to moderate extent only to neurological experiments.

Proposed course of project: (1) Continued volumetric studies of spinal cords after exposure of animals to trauma, x-irradiation, vascular embolization and thrombosis, sero-immunological experiments and conditions of altered oxygen tension. (2) The preparation of the remaining material for continued microscopical examination. (3) The use of histochemical techniques for the clarification of the nature of tissue changes and a comparison between them and those known to occur in the brain. (4) An analysis of dog brains to clarify the cause of hydrocephalus and to classify the changes.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-18
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$15,014	5,322	$20,336	.64	1.36	2.00

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.58	1.42	2.00	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15: NINDB-NA-18
Serial Number

16. PUBLICATIONS:

Cammermeyer, Jan, Volumetric characteristics of spinal cord regions in man, cat, rabbit, and opossum. Anat. Rec., 121: 272, 1955.

Cammermeyer, Jan Changes in volume of spinal cord induced by formalin fixatives. J. Neuropath. & Exp. Neurol., 15: 212, 1956.

Cammermeyer, Jan and W. Haymaker Histological distribution of alkaline glycerophosphatase in the macaque brain following cobalt 60 irradiation. J. Neuropath. & Exper. Neurol. (In press)

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet 1. NINDB-NA-19
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Experimental Neuropathology
SECTION

5. Bethesda

6. Factors involved in the formation of cerebral hemorrhages.
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR

8. Helen Ramsey
OTHER INVESTIGATOR(S)

9. None

101 PROJECT DESCRIPTION:

Objectives: To determine the ways in which petechial hemorrhages occur in the brain.

Methods employed: Histological methods to examine the characteristics of hemorrhages following experimental embolism and thrombosis in rat, rabbit, guinea pig, cat, dog and monkey. Conventional staining procedures to study appearance of neurons, neuroglia, vessels and blood. Study deposition of iron. These studies will be supplemented by physiological

Part A. Project Description (cont'd.)

studies of hemodynamic properties of blood circulation.

Major findings: The histological material of a few cases has been completed; few scattered foci of necrosis and rare hemorrhages were encountered. The remaining of material is almost cut and ready for being stained.

Significance: The analysis of the material collected should provide a basis to determine species and age variation in the reaction of tissue to embolisation and thrombosis. The better understanding of sequence of changes in the tissue, source of iron around the vessels and occurrence of petechial hemorrhages in the brain, will be useful for a correct evaluation of changes occurring in man following cerebral infarction.

Proposed course of project: To subject animals of different species, age and dietary conditions to embolism and thrombosis. Study material histologically and control hemodynamic changes of systemic circulation.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-19
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$14,715	5,218	$19,933	.60	1.20	1.80

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.53	1.27	1.80	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-19
SERIAL NUMBER

16. PUBLICATIONS:

Cammermeyer, Jan,
The significance of cerebral siderosis as an indication of focal permeability to plasma iron. J. Neuropath. and Exper. Neurol., 14:109, 1955.

17. None

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Calendar Year 1956

PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-20
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Experimental Neuropathology
SECTION

5. Bethesda

6. Distribution of fat outside the dura of the spinal cord in mammals.
PROJECT TITLE

7. Helen Ramsey
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATOR(S)

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine factors that permit movements of the vertebral column with neither damage to the spinal cord nor interference with its blood circulation.

Methods employed: A technique was developed to feed animals with a fat soluble dye which after digestion stained the fat of the body. A technique was employed for removal of bone without tearing of fat, dura and cord. The specimens were all being photographed with color to record the appearance of fat.

Part A. Project Description Sheet (cont'd). NINDB-NA-20
SERIAL NUMBER

Major findings: The distribution of extradural fat shows considerable regional and individual variations as examined in around 20 adult cats, 10 kittens and several dogs, guinea pigs, cats and monkeys.

Significance: A systematic review of the distribution of fat is as yet not published but a knowledge of it will be of help for the proper evaluation of factors that contribute to the maintenance of pressure on the spinal cord in normal and disease conditions.

Proposed course of project: To include in the study other species, use of histological techniques and experimental procedures which may help reveal factors controlling the distribution of fat.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-20
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,562	1,621	$6,183	.34	.26	.60

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY '57	.35	.25	.60	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-21
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Experimental Neuropathology
SECTION

5. Bethesda

6. The classification of changes in patients suffering from Refsum's syndrome.
PROJECT TITLE

7. Jan Cammermeyer
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATOR(S)

9. None

10. PROJECT DESCRIPTION:

Objectives: To reveal the changes typical of the condition described by Refsum as Heredopathia atactica polyneuritiformis.

Methods employed: Conventional histological techniques on paraffin embedded material of 4 Norwegian and 1 Swedish case.

Part A. Project Description (cont'd.)

Major findings: 1. Interstitial hypertrophic polyneuropathy including (a) neural muscular atrophy, (b) retrograde atrophy of ventral horns and secondary atrophy of the fasciculi gracili, (c) deposition of fat in the affected peripheral nerves and the fibrotic leptomeninges, and (d) ependymal granulations. 2. Degeneration of brain stem tracts with damage primarily to myelin. 3. Atrophy of inferior olivary nuclei. 4. Reactive changes of sympathetic ganglia.

Significance: 1. Confirm the view expressed by Reese and Bareta (J. Neuropath. & Exper. Neurol., 9:385,1950) that patients with the syndrome of Refsum have suffered from interstitial hypertrophic polyneuropathy of the Dejerine and Sottas type. 2. Clarify the complexity of changes in the peripheral nerves as the result of destruction of myelin in scattered neurons. The nature of damage is herein proposed to proceed as delamination due to a genetical deficiency of the myelin which allows for an easy break of bonds between lipid and protein lamellae. 3. Demonstrate the simultaneous destruction of fiber tracts in the brain stem which indicate that a similar myelin deficiency may operate in the brain.

Proposed course of project: This project is terminated.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-21
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$9,733	3,451	$13,184	.26	.74	1.00

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.20	.80	1.00	

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications 15. NINDB-NA-21
SERIAL NUMBER

16. PUBLICATIONS:

Neuropathological changes in hereditary neuropathies: Manifestation of the syndrome heredopathia atactica polyneuritiformis in the presence of interstitial hypertrophic polyneuropathy. J. Neuropath. & Exper. Neurol., 15:340, 1956.

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-22
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Functional Neuroanatomy
SECTION

5. Bethesda

6. A further study of the auditory afferent and efferent (feed-back) systems including the autonomic innervation of the inner ear.
PROJECT TITLE

7. Grant L. Rasmussen
PRINCIPAL INVESTIGATOR

8. Richard Gacek, Edna P. McCrane, Frank Sordyl
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To reveal unknown anatomical neuronal connections of the great ascending and associated descending auditory pathways in the cat; to learn more about the anatomical and functional interrelationships of these two systems. To continue the anatomico-physiological study of the autonomic innervation of the inner ear about which very little is known.

Major findings: Previous studies by the principal investigator has revealed indications of an orderly system of connecting neurons conducting impulses from the auditory cortex to the cochlea, or organ of hearing. During the past year two new connections of the cochlear nucleus

Part A. Project Description (cont'd)

has come to light by means of degeneration studies. One is a commissural connection between the cochlear nuclei located beneath the floor of the fourth ventricle and the other is a recurrent connection from the cerebellum, which enters the nucleus at its most rostral extremity.

A numerical and fiber caliber analysis of all branches of the vestibular nerve and the cochlear nerve in the macaque monkey, cat and guinea pig has been completed with the major help of Richard Gacek. A study of this sort had not been done and this study was carried out to obtain necessary information for further experimental studies on the autonomic innervation of the inner ear.

Significance: Recent physiological studies by physiologists indicate that the descending auditory system of fibers may exert a regulatory or inhibitory influence on the great ascending system at different nuclear levels and the cochlea itself (Galambos, '56). Elucidation of the anatomical connections of the auditory system will furnish a basis for a more intelligent design of physiological experimentation for interpretation of results leading to an understanding of the hearing mechanism.

Proposed course of project: Important anatomical details of the auditory system remain to be worked out and correlations remain to be drawn with electrophysiological studies carried out in other laboratories. The anatomical and functional role of the autonomic nerves of the inner ear remains unknown and this study will be pursued further.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-22
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
$12,374	4,38[illegible]	$16,7[illegible]0	.7	.[illegible]75	1.[illegible]5

FY'57

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.40	.90	1.30	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NA-22
SERIAL NUMBER

16. PUBLICATIONS:

Gacek, Richard and G. L. Rasmussen A numerical and fiber caliber analysis of the cochlear and the vestibular nerve and its branches of the macaque, cat and guinea pig. (In press.)

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-23
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Functional Neuroanatomy
SECTION

5. Bethesda

6. The precise termination of certain tracts and associated connections of the brain stem and spinal cord.
PROJECT TITLE

7. Grant L. Rasmussen and Leo C. Massopust
PRINCIPAL INVESTIGATOR

8. R. McCrane, J. G. Johnston
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: (a) The initial phase of the fiber tract study is the determination of the origin and termination of the various fiber constituents of the medial longitudinal fasciculus with the aid of newer and more effective experimental techniques; (b) the purpose of another problem is to obtain some factual knowledge about interneuronal relationships which will serve as a basis for gaining a better insight into the phenomenon of facilitation and inhibition at the synaptic level.

Methods employed: (a) Placement of lesions at different levels of the medial longitudinal bundle and its various nuclei of origin and the determination of the neuronal connections of the brain stem and spinal

Part A. Project Description (cont'd.)

cord with the aid of axonal and terminal degeneration methods. (b) Interruption of fibers from different sources which play upon cells of the reticular formation and vestibular nuclei of the cats medulla and to determine the relative loss of terminals about cells and their dendrites as a result of the differently placed lesions. A new highly selective silver stain for synapses, developed in this laboratory, will be employed for this study.

Major findings: Project (a), the study of the medial longitudinal fasciculus has been the major problem of the year requiring the greater amount of time and technical assistance in the preparation of a large series of interrupted serial sections of the brain stem and all levels of the spinal cord. The axonal and terminal degeneration preparations will not be completed until the end of the year, therefore results of this study cannot be reported at this time. Project (b), the study is not sufficiently advanced to report definitive findings at this time.

Significance: Exact knowledge of neuronal connections in most parts of the central nervous system is almost completely lacking, due chiefly to inadequate methods for studying neuronal connections at the synaptic level. The study should furnish information necessary for an understanding of the physiological significance of certain fiber systems of the central nervous system.

Proposed course of project: Project (a), Experiments to be concluded by the end of the year, observations to be completed and manuscript to be prepared for publication. Project (b), to be continued and to be expanded if an additional scientist can be secured.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-23
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$16,485	5,841	$22,326	1.10	.90	2.00

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.75	1.05	1.80	—

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NA-23
SERIAL NUMBER

16. PUBLICATIONS:

Rasmussen, G.L. A more reliable silver method for demonstrating synapses of the central nervous system. Amer. Jour. of Physiol., December, 1956.

Rasmussen, G.L. Selective Silver impregnation of synaptic endings. In press.

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-24
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Functional Neuroanatomy
SECTION

5. Bethesda

6. An anatomico-physiologic study of ascending and descending visceral efferent connections of the brain and spinal cord.
PROJECT TITLE

7. L.C.Massopust, Jr. and G. L. Rasmussen
PRINCIPAL INVESTIGATOR

8. Frank Harrold and J. G. Johnston
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To determine the role played by certain visceral afferent and efferent pathways in the brain stem and spinal cord in such visceral functions.

Methods employed: (a) Lesions were placed in various visceral nuclei and fiber tracts of the brain stem of cats. After 6 to 7 days the animals were autopsied, cut and stained with the Nauta silver technique. Serial sections are being studied to evaluate the course, connections and terminations of various visceral pathways.

(b) Physiological studies were made on the temperature regulatory ability of rats and cats through the use of temperature recorders. These recorders made simultaneous records of skin rectal and brain temperatures over any period of time used as a test.

Part A. Project Description (cont'd.)

Major Findings: (a) Destruction of the medial longitudinal fasciculus is believed by some investigators to interconnect the hypothalamus and midbrain with the sympathetic intermedio-lateral cell groups of the spinal cord. Results of our degeneration experiments do not confirm this viewpoint. Experiments are in progress dealing with descending visceral connections of the hypothalamus and lower brain stem but are too incomplete to report on at this time. (b) a vital area which when surgically damaged alters the temperature regulatory ability of rats has been located traversing the spinal cord in the region of the lateral grey columns.

Significance: This project will provide basic information as to how the central nervous system functions in its control over certain visceral functions such as temperature regulation, fever, pain, shivering, panting and others.

Proposed course of project: To continue the foregoing investigation in an attempt to trace the pathways involved in certain visceral functions mentioned above. To continue to rule out or establish certain "presumed" connections which are said to have a part in the control of these visceral functions.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-25
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Functional Neuroanatomy
SECTION

5. Bethesda

6. The role of the hypothalamus and other areas of the brain stem on temperature regulation.
PROJECT TITLE

7. L. C. Massopust, Jr.
PRINCIPAL INVESTIGATOR

8. Frank Sordyl
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: (a) The determination of stereotaxic coordinates on the brain stem of the rat. (b) To place discrete lesions in the brain stem of the rat and evaluate the effect of such lesions in temperature regulatory ability.

Methods employed: The determination of stereotaxic coordinates in the rat brain was accomplished through the use of standard Horsley-Clark methods.

Major findings: A universal atlas for use on any standard Horsley-Clark stereotaxic instrument adaptable for the rat has been

Part A. Project Description (cont'd.)

completed. This atlas has been accepted for publication in a monograph: "Electrical Stimulation of the Brain" financed by the Hogg Foundation of Houston, Texas. Preparation of the manuscript and plates is now underway.

Proposed course of project: Part (a), the technical part, has been completed. Part (b) has been transferred to another project and investigations are being continued. A related project reported last year, has been temporarily discontinued until certain morphological studies, now included in a different project, have been completed.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NA-2[illegible]
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57 $7,[illegible]	2,765	$10,567	.50	.50	1.00

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57 .50	.50	1.00	—

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NA-26
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Functional Neuroanatomy
SECTION

5. Bethesda

6. Origin and termination of the frontopontine tract.
PROJECT TITLE

7. Grant L. Rasmussen
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATOR

9. None

10. PROJECT DESCRIPTION:

Objectives: (a) To determine whether or not the frontopontine tract possesses fibers of sub-cortical origin. (b) To trace fiber components to termination in pons and elsewhere.

Methods employed: Performance of total and subtotal hemispherectomies in monkeys, preferably chimpanzee; placement of lesions in the cerebral peduncle; determination of the origin, course and endings of the fibers by means of suitable neuropathological techniques.

Major findings: No progress made during past year due to lack of suitable human and experimental monkey material.

Part A. Project Description (cont'd.)

Significance: Observations resulting from this project should (a) add to our knowledge regarding the origin and termination of this tract; (b) form a basis for subsequent physiological studies of its function and (c) lead to an understanding of the results obtained in humans after section of the frontopontine tract as is practiced in certain neurological procedures.

Proposed course of project: To continue this project when suitable human hemispherectomy specimens or higher primate experimental material can be obtained.

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Part B. Budget Data

11. NINDB-NA- 26
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$10,418	3,690	$14,108	.40	.80	1.20

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
.40	.80	1.20	—

FY'57

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB M-3 OD-7
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration (Puerto Rican Cooperative Project)
SECTION

5. San Juan

6. Relation of adverse factors in the perinatal period in neurological and psychological deficits--Monkeys
PROJECT TITLE

7. C. J. Bailey
PRINCIPAL INVESTIGATOR

8. José Frontera, Marisa I.R. Ramirez de Arellano, Carroll A. Pfeiffer John O. Smart and Stuart Altmann
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: To institute a cooperative research project on the subject indicated in the title. These studies will be related to those reported in project NM 9 but will involve the rhesus monkey. Although a number of adverse factors of the perinatal period will be examined, asphyxia neonatorum or anoxia soon after birth of the monkey will be the subject of the initial investigation.

Methods employed: Female monkeys in a caged colony will be paired with compatible males for breeding. Some infants will be delivered without attempting to induce anoxia or other adverse conditions.

Part A. Project Description (cont'd.)

Siblings will be asphyxiated at or before birth. Their postnatal behavior will be studied, they will be subjected to neurological examinations, utilizing the EEG, etc., and will be given certain learning tests.

There are many behavioral tests that can be given to rhesus monkeys. Since each test involves original learning, as well as later utilization, of a habit, two scores for each are available. Training in simple conditioning can be begun in the first week of life. In the first month, monkeys will perform in straight runways and in single choice-point mazes. Slightly later, devices involving lever-pressing, chain-pulling and wheel-rotation can be used. Before the infant is three months old, training in complex alternation and delayed response problems can be started. By adding discrimination features to any of these tasks, testing of sensory capacities is possible. All of these tests involve the motor system, but purer measures of motor capacities can be obtained by testing general activity or specific, manipulation, activity. Training in these tasks can be begun very early, but since some of them require considerable practice to master, tests of retention will be delayed until adolescence.

Eventually the animals will be killed and the nervous system studied. Correlations will be drawn between the physiological, psychological and anatomical observations.

Major findings: Considerable effort has gone into the organization of the project, constructing and equipping of a laboratory of perinatal physiology in San Juan, and rehabilitation of the free range colony of rhesus monkeys on Cayo Santiago. A caged colony of approximately 60 breeding rhesus monkeys has been acquired and is about to be installed in the San Juan laboratory. The project is organized in such a way that the studies will involve cooperation between certain members of the Laboratory of Neuroanatomical Sciences, now resident in San Juan, and certain members of the Laboratory of Anatomy, Medical School, University of Puerto Rico.

A conference on the subject, "Asphyxia Neonatorum, Brain Damage and Impairment of Learning", particularly as it applies to animals, was held the end of August in San Juan. The transactions of this conference are being edited to form a monograph which will be published.

Considerable progress has been made toward rehabilitation of the free range breeding colony of 200 Macacca mulatta monkeys on Cayo Santiago. The animals are now being adequately fed a new type of food

NINDB ~~NA-2~~ CD-7
SERIAL NUMBER

Part A. Project Description (cont'd.)

at multiple stations throughout the island. A new water supply has been installed. It is hoped that the effect of this will be to break up the one large group of monkeys into tribes, each dominated by one male. The breeding potential of the colony thus is expected to be enhanced.

Studies of behavior are being carried out on the free range colony of monkeys during the transition from the one large disorganized group of monkeys to a new tribal existence.

Significance: Present study helps form the basis for understanding certain neurological and psychological deficits in the human being which may result from adverse factors in the perinatal period. It has direct bearing on the cause and prevention of cerebral palsy, mental retardation, certain types of epilepsy, deafness and blindness.

Proposed course of project: Last year was one of organization; during the next year, it is expected that experiments will get under way.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB ~~NA - 2~~ OD-7
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY '57	~~$ 32,200~~	1,892	$40,312	.55	1.47	2.02
	BUDGETED POSITIONS			PATIENT DAYS		
	PROF	OTHER	TOTAL			
FY '57	.75	2.00	2.75	—		

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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INDIVIDUAL PROJECT REPORT

Part C.: Honors, Awards & Publications

15. NINDB ~~NA-2700~~ 700-7
SERIAL NUMBER

16. PUBLICATIONS:

Bailey, C. J. and W. F. Windle, (1956) Interrelationship of Asphyxia Neonatorum, Cerebral Palsy and Impairment of Learning. Pediatrics (in press).

Windle, W. F. (1956). Neurological and Psychological Deficits of Asphyxia Neonatorum. U.S.P.H.S. Reports, (in press).

17. NONE

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-~~AA-~~00-8
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neuroanatomical Sciences
LABORATORY

4. Development and Regeneration
SECTION

5. Bethesda

6. Development of Behavior and Communication in the Macaca mulatta under free range conditions.
PROJECT TITLE

7. Stuart Altman
PRINCIPAL INVESTIGATOR

8. C. J. Bailey and John Smart
OTHER INVESTIGATOR(S)

9. None

10. PROJECT DESCRIPTION:

Objectives: (a) To study physical development and development of social behavior in rhesus monkeys under free range conditions on Cayo Santiago.

(b) To study the means by which animals have learned to communicate with each other under the conditions of (a).

Methods employed: Motion picture recording and sound recording, by means of special equipment which concentrates distant sound with parabolic reflectors, amplifying it and playing into a tape recorder. Visual observation on undisturbed

Part A. Project Description (cont'd).

monkeys and anthropometric measurements on captured animals to collect data on physical development.

Major findings: Project is just beginning. There has been one roundup of monkeys on Cayo Santiago. They have been weighed, measured and tatooed for future identification. Measurements have been made on some animals soon after birth and during the first year of life as well as on older specimens. Work on the physical facilities of Cayo Santiago is nearing completion.

Significance: It is expected that behavioral study of the rhesus monkey may serve as a baseline and normal control for similar studies on caged monkeys of the same species. The latter studies will be carried out in the Laboratory of Perinatal Physiology in San Juan. So far as we know there have been no comparable studies of monkeys under free range conditions. The project should have considerable significance in terms of human social behavior, though this is not the primary objective.

Observations of birth of the monkeys, of mating, and of what constitutes compatibility between males and females may be of value to our efforts to breed monkeys in caged colonys. Observations of the care of the infant by the mother under natural conditions may be of value to our project in the caged colony in helping determine how best to care for the infants who are taken away from the mother either by Cesarean section or immediately after natural birth.

Proposed course of project: To develop the facilities for the study and to carry out the study in the manner outlined above.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-~~NA-28~~ OD-8
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$38,500	1,892	$40,392	.05	1.1	1.2

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	5			—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC1
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Biosynthesis of Complex Cerebral Lipids
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: Investigation of the formation of complex cerebral lipids containing sphingosine.

Objectives: To elucidate the pathway of formation of sphingolipids and to determine the rate of turnover and fate of these substances.

Methods employed: A new analytical method for the isolation and purification of sphingosine has been developed by this laboratory. With the use of this technique, experiments will be conducted with appropriate C^{14}-labeled materials to investigate the biosynthesis of sphingosine and to establish the nature of the enzymes and co-factors required for this process.

Major findings: New analytical methods for the isolation of sphingosine have been developed and suitable chromatographic procedures have been devised and tested for separating newly synthesized products from the starting materials of the reaction mixtures. Biosynthetic studies have not been undertaken as yet.

Significance to Neurological Diseases research: Since a major portion of brain lipids, including myelin, contain sphingolipids, it is most desirable to learn something of the biosynthetic pathways and factors which control these reactions. This latter information is particularly important since certain conditions such as Gaucher's Disease and Tay-Sachs Disease are associated with a superabundance

of cerebrosides and gangliosides respectively. Other diseases such as multiple sclerosis exhibit characteristic destruction and loss of myelin, and it is obviously extremely desirable to learn the nature of the factors which cause these conditions.

Proposed course of project: A suitable source of material for the preparation of the appropriate enzymes must be found by investigating the rate of formation of sphingolipids under various conditions in vivo. The choice of the proper animal and age must be determined. When this information is available, an attempt will be made to study the biosynthesis of sphingosine in broken-cell preparations in vitro and the enzymes and co-factors involved in this process purified and identified. It will probably be necessary to prepare C^{14}- or P^{32}-labeled sphingosine for studies on the incorporation of this material into sphingomyelin and cerebrosides.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NC1
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$3,970	1,399	$5,369	.20	.25	.45

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.20	.25	.45	—

13. BUDGET ACTIVITY: RESEARCH

14. NONE

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Part C: Honors, Awards & Publications

15. NINDB-NC1
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Brady, R.O. and Burton, R.M., Purification and Properties of Sphingosine, J. of Neurochemistry, 1, 18 (1956).

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC2
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Microdetermination of Enzymatic Decarboxylation in Selected Samples of Brain Tissue
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATORS

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: Investigation of enzymatic decarboxylation of glutamic acid.

Objectives: We wish to learn the distribution of certain decarboxylating enzymes in specific cells and areas of the brain.

Methods employed: A suitable ultramicroanalytical technique has been successfully developed which permits the utilization of microgram quantities of brain tissue for the estimation of specific decarboxylating enzymes.

Major findings: The feasibility of the ultramicro method has been proved by suitable preliminary experiments.

Significance to Neurological Diseases Research: Amines such as γ-amino butyric acid and 5-hydroxytryptamine are found in significant concentrations in brain tissue. The latter compound has been implicated as a neurohumoral agent by some investigators. We should like to examine the distribution of specific enzymes which catalyze the formation of these compounds and to try to assess the physiological significance of these processes.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NC2
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$4,787	1,687	$6,474	.16	.25	.41

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.16	.25	.41	

13. BUDGET ACTIVITY: RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957.

Dr. Wayne Albers, Laboratory of Neuroanatomical Sciences, NINDB.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC3
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Woods Hole, Massachusetts
LOCATION

6. Intra-Axonal Injection of Enzymes and Co-factors
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8. [illegible]
OTHER INVESTIGATORS

9. NINDB-NP3

10. PROJECT DESCRIPTION:

Project: Investigation of the effect of the intra-axonal injection of certain enzymes and key intermediary compounds on nerve conduction.

Objectives: We wish to continue studies of the effects of the intra-axonal injection of key enzymes which appear likely to be involved in the production and maintenance of the resting potential and the conduction of nerve impulses.

Methods employed: A suitable microinjection technique has been developed, and for the first time the intra-axonal injection of enzymes has been successfully accomplished. We propose to continue to explore the effects of the injection of certain critical materials employing this technique.

Major findings: We have found that the process of nerve conduction and maintenance of resting potential does not appear to be immediately related to acetyl choline; i.e., conduction was uninfluenced by injecting acetyl choline over a wide range of concentrations, by injection of a large excess of the enzyme cholinesterase, or by the injection of a potent cholinesterase inhibitor nerve gas, diisopropyl phosphofluoridate. We have performed similar critical studies with carbonic anhydrase, adenosine triphosphatase, and diphosphopyridine nucleotidase, and have found them to be

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Part A. Project Description Sheet, continued NINDB-NC3
SERIAL NUMBER

without effect. We have observed that certain preparations of derivatives of coenzyme A do block nerve conduction. Also, certain amines such as glutamine, guanidine, and [redacted] ammonium chloride bring about changes in the action potential of the conducted impulse.

Significance to Neurological Diseases Research: Fundamental studies such as these are potentially of utmost significance to Neurological Disease research, since the biochemical mechanisms involved in nerve transmission are only vaguely understood. We wish to try to establish the nature of the reactions which create the membrane resting potential and are responsible for nerve conduction.

Proposed course of project: The studies already undertaken will be continued and specific attempts will be made to establish the nature of the inhibition by coenzyme A derivatives by use of suitable control experiments which were not available previously due to the exploratory nature of the original studies. A more complete investigation of the profound effects exhibited by certain amines must be undertaken and experiments designed to elucidate the nature of the effect of reactive amines will be performed.

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Part B: Budget Data

11. NINDB-NC3
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,743	2,024	$7,767	.34	.25	.59

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.34	.25	.59	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NCL
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Effect of Lysergic Acid Diethylamide on Enzymatic Reactions
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8. Richard Salvador, Guest Worker
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: Investigation of the influence of lysergic acid diethylamide (LSD) on enzymatic reactions.

Objective: To learn something of the mechanism of action of the compound upon the cerebral cortex and to continue investigations of the metabolism of this material.

Methods employed: The effect of LSD will be determined upon specific enzyme systems obtained from brain tissue. An attempt will be made to solubilize enzymes found in microsomal particles which catalyze the hydroxylation of LSD.

Major findings: The metabolism of LSD has been investigated, and an enzyme system was found in microsome preparations from liver which causes the hydroxylation of LSD at position 2 of the indole ring. This enzyme system requires reduced triphosphopyridine nucleotide and molecular oxygen. The product of the reaction, 2-oxy LSD, does not exhibit any psychological or pharmacological activity.

LSD has been injected directly into the squid giant axon and was found to be entirely without effect upon conduction of nerve impulses in this preparation.

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Part A. Project Description Sheet, Continued

NINDB-NCL
SERIAL NUMBER

Significance to Neurological Diseases Research: If one can discover [redacted]ffect of LSD upon specific metabolic processes, it is possible that some significant insight may be obtained about the nature of metabolic derangements in schizophrenia if such aberrations do exist. Thus, there would become available a potentially valuable break-through into studies of psychoses. It might be possible to by-pass the effected metabolic reaction by supplying a supplementary quantity of the attenuated metabolite or attempt to displace the offending compound by the judicious administration of competitive inhibitory materials.

Proposed course of project: Techniques for the use of microgram quantities of brain tissue will be perfected, and the effect of LSD will be studied on enzyme systems obtained from selected areas of brain known to be influenced by LSD; e.g., the lateral geniculate nucleus and the retina. [redacted] techniques for the selective disruption of microsomes will be investigated and an attempt made to solubilize and characterize the enzymes responsible for the hydroxylation of LSD.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NCB
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,943	2,024	$7,967	.33	.25	.58

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.25	.58	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NCL
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Axelrod, J., Brady, R.O., Witkop, B., and Evarts, E.V., Metabolism of Lysergic Acid Diethylamide, Nature, 178, 143 (1956).

Axelrod, J., Brady, R.O., Witkop, B., and Evarts, E.V., Distribution and Metabolism of Lysergic Acid Diethylamide, Ann. New York Academy of Science, in press.

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC5
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Biosynthesis of Cerebrosides
PROJECT TITLE

7. Robert M. Burton
PRINCIPAL INVESTIGATOR

8. Roscoe Brady
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: Investigation of the enzymatic synthesis of cerebrosides.

Objectives: We wish to discover the pathway for the biological synthesis of cerebrosides and related compounds such as gangliosides.

Methods employed: Standard enzymatic techniques have been used employing C^{14}-labeled substrates as starting materials for the biosynthesis of cerebrosides. A new method has been developed for the preparation of analytically pure sphingosine, one of the major constituents of the cerebroside molecule.

Major findings: It has been necessary to do prolonged experiments in vivo to establish the optimal animal source, age, and tissue to be employed for a detailed examination of the pathway of cerebroside biosynthesis in vitro. These experiments have been completed and constitute a fundamental contribution to the problem since a direct result of these findings has been the demonstration for the first time of the biosynthesis of cerebrosides in vitro employing isolated sub-cellular elements of brain tissue.

Significance to Neurological Diseases research: We are now on the threshold of examining the exact mechanism and pathway of cerebroside biosynthesis. Knowledge of this pathway and of the factors which exert an influence upon the rate of this process should provide extremely important fundamental information

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Part A. Project Description Sheet, Continued

NINDB-NC5
SERIAL NUMBER

regarding the process of myelination. It is hoped that this information will enable us to make judicious selections of therapeutic agents for conditions such as Gaucher's and Tay-Sachs' Disease or demyelinating diseases such as multiple sclerosis.

Proposed course of project: A detailed examination of cerebroside synthesis in vitro will be carried out. We shall attempt to discover the location and nature of the enzymes involved in the process, to identify the intermediary steps in the reaction sequence, and to establish the identity of any co-factors which may be required. It is likely that C^{14}-labeled intermediary compounds, particularly sphingosine and ceramides, will have to be prepared by synthetic organic chemical methods in order to establish accurately the extent of the participation of these materials in cerebroside biosynthesis.

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Part B: Budget Data

11. NINDB-NC5
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$7,384	2,604	$9,988	.33	.59	.92

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.59	.92	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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Part A. Project Description Sheet

1. NINDB-NC6
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. The Relationship of Nucleotides to Lipid Synthesis
PROJECT TITLE

7. Robert M. Burton
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. [redacted]

10. PROJECT DESCRIPTION:

Project: Nucleotides involved in the synthesis of complex lipids.

Objectives: Many of the reactions involved in the synthesis of the complex lipids of nervous tissue are probably mediated by enzyme systems requiring nucleotide coenzymes for hydrogen transfer, i.e., di- and tri-phosphopyridine nucleotides and flavin adenine dinucleotide, as well as coenzymes required for energy transfer, i.e., adenosine di- and tri-phosphates, phosphate esters of other purine and pyrimidine bases, and coenzyme A. An understanding of the relationship of these nucleotide coenzymes to complex lipid synthesis and degradation may provide a valuable clue to metabolic lesions associated with certain lipidoses.

Methods employed: The usual enzymatic techniques employed for studying enzyme systems will be used, i.e., spectrophotometry, manometry, fluorimetry, and radioisotope-labeled compounds.

Major findings: It has been found that galactose incorporation into the cerebroside fraction of rat brain tissue occurs primarily during the second and third week post partum (NINDB-NC5). Studies have shown that the pyridine nucleotide (PN) concentration and the diphosphopyridine nucleotidase (DPNase) activity of rat brain tissues increases at a rapid rate during this period. Following the third week, the concentration of PN and DPNase was found to

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Part A. Project Description Sheet, Continued

NINDB-NC6
SERIAL NUMBER

remain relatively constant. The PN concentration increased two-fold during this period when computed on a wet tissue weight basis, while the DPNase activity showed a 10-fold increase. Nicotinamide stimulated in vivo synthesis of PN was slightly greater in the 25-day old rat as compared to the 8-day old animal. In vitro experiments have shown that various pyridine derivatives, including 3-acetyl pyridine, can form analogs of PN by an exchange reaction catalyzed by brain DPNase. We have found that 3-acetyl pyridine was more toxic to the older animal (25-day old) than to the young (8-day old). This increase in toxicity may possibly be related to the higher DPNase activity in the brain tissue of the 25-day old rat and therefore to a greater possibility of forming a PN analog. It has been observed in preliminary experiments that reserpine apparently retards the rate of nicotinamide stimulated in vivo synthesis of PN. Even though the PN synthesis was slowed, a higher final PN level was obtained and maintained longer with reserpine-treated mice than with vehicle-injected controls.

Significance to Neurological Diseases Research: Certain diseases of the nervous system are characterized by the over-production of complex-lipids, e.g., gangliosides in Tay-Sachs disease. Studies of this nature should lead to an understanding of the normal synthesis of these lipids and may lead, therefore, to a knowledge of the metabolic lesion responsible for either the over-production or the decreased rate of metabolism of these lipids in various nervous disorders.

Proposed course of project: Studies will be continued to determine the concentration, rate of synthesis, and rate of destruction, of these nucleotides in animals during the development of the nervous system and myelination. This will be correlated with oxidative reactions of brain tissue and with the rate of lipid synthesis. Finally, the individual enzyme systems involved will be isolated, characterized, and their properties described.

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Part B: Budget Data

11. NINDB-NC6
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$5,057	1,782	$6,839	.34	.25	.59

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.34	.25	.59	

13. BUDGET ACTIVITY: RESEARCH

14. None

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Part A. Project Description Sheet

1. NINDB-NC7
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Toxicity of Neurophysiologically Active Chemicals
PROJECT TITLE

7. Robert M. Burton
PRINCIPAL INVESTIGATOR

8. Abraham Goldin
OTHER INVESTIGATORS

9. This project complements research being carried out by the Laboratory of Chemical Pharmacology, National Heart Institute.

10. PROJECT DESCRIPTION:

Project: Mechanisms involved in the toxicity of neurophysiologically active agents.

Objectives: The mechanisms through which neurophysiological agents such as marsilid and reserpine exert their toxic properties are unknown. It is hoped by studying the relationships of these agents, at toxic doses, to other compounds which give protective action, that some of the underlying biochemical mechanisms may be elucidated. These relationships will serve, thereby, as a guide to the investigation of the individual enzyme systems that may be affected.

Methods employed: In vitro studies will be carried out by the techniques and methods commonly used for investigating enzyme systems, i.e., spectrophotometry, manometry, and radio-isotopic procedures. In vivo experiments will be performed by classical pharmacological techniques.

Major findings: Toxic doses of reserpine produced a depression or stupor in mice characterized by a physical state resembling sleep, with failure to respond to stimuli such as noise and prodding. The mice retained their righting-reflex which, therefore, distinguishes the reserpine-depressed state from anesthesia. Under similar conditions, chlorpromazine and pentobarbital produced anesthesia. d-amphetamine, d-deoxyephedrine, d-lysergic acid diethylamide (d-LSD), and

d-lysergic monoethylamide (LAE) were potent analeptics for the reversal of reserpine-sedation. l-amphetamine, l-LSD, and 2-bromo-d-lysergic acid diethylamide (BOL-148) showed little or no capacity for arousing the reserpine-depressed mice. Dose-response curves were obtained relating the duration of analeptic action to the amount of drug administered. d-amphetamine, d-deoxyephedrine, and d-LSD demonstrated some analeptic activity when given to chlorpromazine-treated mice. However, these mice were sluggish in contrast to the alert, active state produced with the reserpine-sedated mice. None of these analeptics were effective when administered to pentobarbital-anesthesized mice. Both d-LSD and BOL-148 were able to antagonize the property of serotonin to prolong barbiturate anesthesia. d-LSD, but not BOL-148, was able to antagonize the prolongation of barbiturate anesthesia by reserpine. The results suggest that the action of reserpine to produce sedation and to prolong anesthesia may not be mediated via serotonin. Under certain conditions, d-LSD, itself, has been shown to be able to prolong barbiturate anesthesia. BOL-148 did not produce an increase in the duration of pentobarbital anesthesia. Pentobarbital has been demonstrated to inhibit competitively the enzymatic hydroxylation of d-LSD *in vitro*.

Reserpine has been shown to favorably alter the course of acute lymphoid leukemia, L1210, in mice. Leukemic mice treated with reserpine survived for an average of 8.6 ± 1.2 days, whereas untreated or vehicle-treated controls died of leukemia after 2.6 + 0.3 days. The local tumors present in the leukemic mice decreased from about 11 mm. in diameter, at the time treatment was initiated, to such an extent that they could not be detected by palpation on the eighth day following treatment. Serotonin administration was not effective as an anti-leukemic agent under these conditions. Comparable food and water restriction in control animals with advanced leukemia failed to diminish the growth of the local tumor or to increase the survival time of the mice, as compared to controls which received food and water *ad lib*.

Significance to Neurological Diseases Research: Studies of the inter-relationships that exist between the actions of drugs, whether the relationship is one of potentiating the action of another drug or of protecting the organism against the toxic manifestation of certain compounds, may prove to be fruitful for obtaining an understanding of basic physiological and biochemical processes. An understanding of the mechanism of action of neurologically active drugs, such as reserpine, could give an important insight to the fundamental biochemistry involved in neurological diseases.

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Part A. Project Description Sheet, Continued

NINDB-NC7
SERIAL NUMBER

Proposed course of project: Studies will be continued to correlate structure and physiological response of those drugs that are potentiated by reserpine and related compounds, and, in particular, those compounds that will protect the host against the toxic manifestations of the neurophysiologically active agent. In vitro studies will be undertaken to investigate possible biochemical sites of action of these compounds. A more detailed investigation of the biochemical action of reserpine as an anti-leukemic agent will be completed.

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Part B: Budget Data

11. NINDB-NC7
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,057	1,782	$ 6,839	.33	.25	.58

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.33	.25	.58	—

13. BUDGET ACTIVITY: RESEARCH

14. This project is being carried out cooperatively with the Section on Biochemical Pharmacology, Laboratory of Chemical Pharmacology, National Cancer Institute.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC8
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Metabolism of Inositol
PROJECT TITLE

7. B.W. Agranoff
PRINCIPAL INVESTIGATOR

8. Roscoe Brady
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: Investigation of the metabolism of inositol.

Objectives: To learn the nature of the biosynthetic pathway for the formation of brain diphosphoinositides.

Methods employed: A suitable quantitative analytical method has been developed for the determination of inositol. Using this method, the uptake of inositol by tissue slices of various organs of several species of animals has been determined. We are now in the process of preparing tritium-labeled inositol.

Major findings: Surviving tissue, such as brain and testes, liberate inositol into the incubation medium, whereas kidney slices show a pronounced uptake of inositol from the medium. These findings have been reported in brief at the Symposium on the Chemistry and Biochemistry of the Cyclitols, Atlantic City, N.J., September 20-21, 1956.

Significance to Neurological Diseases Research: These findings represent the preliminary steps towards the major endeavor of this project which is to discover the mechanism of brain inositide biosynthesis. Since the phosphorous of brain phosphoinositide exhibits a very rapid turnover, it seems likely that these compounds represent important brain components not only from a structural aspect but participate actively in cerebral metabolic processes.

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Part A. Project Description Sheet, Continued

NINDB-NC8
SERIAL NUMBER

Proposed course of project: It is quite imperative that inositol labeled with C^{14} or T^{3} be prepared in order to investigate the pathway of inositol incorporation into complex lipids of the brain. We shall attempt to identify and characterize the enzymes and co-factors involved and to learn something of the factors which influence and control this process.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NC8
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$6,699	2,362	$9,061	.33	.58	.91

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.33	.58	.91	

13. BUDGET ACTIVITY: RESEARCH

14. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NC8
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

This project is an outgrowth of a study of ribose metabolism. An enzyme responsible for the initial phosphorylation of ribose has been discovered and characterized. A report of these findings has been published.

Agranoff, B.W. and Brady, R.O., Purification and Properties of Calf Liver Ribokinase, J. Biol. Chem., 219, 221 (1956).

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC9
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Biochemistry of Neuraminic Acid
PROJECT TITLE

7. [redacted]
PRINCIPAL INVESTIGATOR

8. [redacted]
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: Investigation of the biological significance and biosynthesis of neuraminic acid.

Methods employed: Spectrophotometric methods as well as radioactive tracers will be used in whole animals as well as preparations derived from broken cells in an effort to establish the method of biosynthesis of this carbohydrate and its participation in the formation of complex cerebral lipids.

Main findings: New project

Significance to Neurological Diseases Research: Neuraminic acid levels have been found to be elevated in the brain lipids in Tay-Sachs disease, a degenerative neurological disease of children. Obviously, information regarding the pathways of metabolism of this compound is of considerable interest in this condition. Furthermore, gangliosides, which contain neuraminic acid, are normal constituents of brain tissue, and a logical extension of this project leads to an investigation of the metabolism of this complex lipid material.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet, Continued

NINDB-NC9
SERIAL NUMBER

Proposed Course of project: Since milk is a rich source of neuraminic acid for growing animals, preliminary investigations of the biosynthesis of neuraminic acid will be undertaken employing tissue preparations obtained from lactating animals. It may become necessary to prepare C^{14} or T^{3}-labeled neuraminic acid in order to decide if this component of gangliosides is synthesized by brain elements in situ or must be obtained from exogenous sources. It is hoped that the pathway of incorporation of neuraminic acid into ganglioside will be elucidated.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NC9
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,239	1,494	$5,733	.41	—	.41

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.41	-	.41	—

13. BUDGET ACTIVITY: RESEARCH

14. None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC10
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Metabolism of Meprobamate
PROJECT TITLE

7. J. W. Agranoff
PRINCIPAL INVESTIGATOR

8. Julius Axelrod
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Objectives: Investigation of the physiologic disposition of meprobamate (Miltown-equanil).

Methods employed: A method for the direct determination of meprobamate in biological fluids has been developed. We will use this method to ascertain the pathways of meprobamate metabolism.

Main findings: In preliminary studies, we have found that over 15% of injected meprobamate was excreted unchanged in the urine. An additional amount was excreted in the bound form which has not been identified as yet.

Significance to Neurological Diseases Research: The mechanism of action and mode of excretion of meprobamate are not yet known. Information on this subject should prove valuable towards improving our understanding of this new class of drugs which affects the central nervous system.

Proposed course of project: Excretion patterns will be studied. We will attempt to determine the nature of the conjugated urinary product and site and mechanism of its formation. The distribution of this material in various tissues will be studied.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NC10
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$4,239	1,494	$5,733	.41	—	.41

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	41	—	.41	—

13. BUDGET ACTIVITY: RESEARCH

14. Dr. Julius Axelrod, Clinical Investigations, NIMH

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC11
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Metabolism of Derivatives of Coenzyme A
PROJECT TITLE

7. Wilscoe Brady
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: Investigation of the occurrence and properties of cysteamine oxidase.

Objectives: A new enzyme has been discovered in extracts of certain tissues which catalyzes the oxidation of 2-mercaptoethylamine. The specificity and properties of this enzyme have been ascertained.

Methods employed: Standard enzyme fractionation procedures were used to purify the enzyme. The product of the reaction was identified by using S^{35}-labeled cysteamine as substrate.

Major findings: Partial purification of an enzyme present in extracts of pigeon liver acetone powder has been accomplished. The substrate specificity was examined, and it was found that cysteamine was oxidized most rapidly. N-acetyl cysteamine was oxidized at one-tenth the rate of cysteamine and coenzyme A about one-fiftieth as rapidly. Cystamine was not oxidized, hence it appears likely that the formation of taurine from cysteamine requires several specific enzyme-catalyzed steps. Metal and nucleotide requirements for cysteamine oxidase were investigated and the effects of various chelating agents have been examined.

Significance to Neurological Diseases Research: These studies were undertaken with a two-fold objective, to investigate the possible enzymatic oxidation of coenzyme A which is indispensable for the biosynthesis of fatty acids and to study the pathway of the

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet, Continued

NINDB-NC11
SERIAL NUMBER

formation of taurine which is a major sulfur-containing constituent of brain tissue. Some direct information concerning both of these processes has been obtained and considerable data has been accumulated which has very fundamental application regarding the nature of protein and chelating substances in biochemical oxidation reactions which exhibit a requirement for a metal ion. These studies provide basic information regarding the kinetics and mechanism of the formation of various brain constituents such as long chain fatty acid and taurine.

Proposed course of project: This particular aspect of the study of factors which influence the biosynthesis of lipids was completed on July 1, 1956.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NC11
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$4,239	1,494	$5,733	.41	—	.41

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.41	-	.41	

13. BUDGET ACTIVITY: RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957.

Dr. Richard Salvador, Department of Pharmacology, The George Washington University School of Medicine.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NC11
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Salvador, R. and Brady, R.O., Cysteamine Oxidase, Federation Proceedings, 15, 345 (1956).
Salvador, R., Thesis, Doctor of Philosophy, The George Washington University School of Medicine, 1956.
Brady, R.O., Enzyme-catalyzed Transfer Reactions of Thiol Esters. Symposium sur la Biochimie de Soufre, Roscoff, France, May 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Brady, R.O. Recipient of a special travel award from the French National Center of Scientific Research to participate in a colloquium on the biochemistry of sulfur. Roscoff, France, May 1956.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC12
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Lipid Chemistry
SECTION

5. Bethesda, Maryland
LOCATION

6. Biosynthesis of Fatty Acids
PROJECT TITLE

7. Roscoe Brady
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION:

Project: To investigate the mechanism of the stimulating effect of citric acid on the biosynthesis of fatty acids.

Objectives: To discover the nature of the stimulating effect of citrate on fatty acid synthesis.

Methods employed: Fatty acid synthesis was accomplished by incubating suitable water-soluble enzyme preparations with C^{14}-labeled sodium acetate. Suitable additional spectrophotometric and manometric analytical techniques were employed for supplemental analyses.

Major findings: The biosynthesis of long-chain fatty acids is markedly stimulated by the addition of a continuous supply of reduced triphosphopyridine nucleotide (TPNH). Furthermore, fatty acid synthesis is inhibited by the presence of a slight excess of free coenzyme A, whereas fatty acid oxidation is stimulated by added coenzyme A. Both processes are dependent upon the presence of an adequate amount of coenzyme A. It has been found that in diabetes or starvation, tissue levels of coenzyme A are significantly higher than in the normal fed animal. Furthermore, in fasting or diabetes, there is a shift in the pathway of glucose catabolism in the liver from a preponderance of the hexose monophosphate oxidative route which yields TPNH early in the sequence of reactions towards the Embden-Myerhof glycolytic pathway which lacks a TPNH generating reaction. These observations are consistent with the

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INDIVIDUAL PROJECT REPORT

Part A., Project Description Sheet, Continued

NINDB-NC12
SERIAL NUMBER

findings of markedly impaired fatty acid synthesis in diabetes and fasting in the presence of at least normal rates of fatty acid oxidation and appear to shed considerable light upon the biological regulation of fatty acid metabolism.

Significance to Neurological Diseases Research: These studies constitute significant contributions to the over-all research projects under investigation in the laboratory. We now know some of the important factors which are required for the biosynthesis of lipids which constitute the major non-aqueous component of nerve tissue. Long-chain fatty acids form an integral part of cerebrosides, sphingomyelins, and ganglioside of nerve tissue and hence information regarding the control of their metabolism is of potential importance in the biosynthesis and metabolism of all of these complex lipids.

Proposed course of project: This particular aspect of the biosynthesis of complex lipids has been successfully completed. Data obtained in these experiments will contribute significantly to studies on the synthesis of complex lipids described in a separate project report.

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INDIVIDUAL PROJECT REPORT

Part B. Budget Data

11. NINDB-NC12
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	$5,743	2,024	$7,767	.37	.33	.70

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.41	.33	.74	

13. BUDGET ACTIVITY: RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957.

Mr. Abdel Megid Mamoon, Guest Worker, National Research Council of Egypt.

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards & Publications

15. NINDB-NC12
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

Brady, R.O., Mamoon, A.M., and Stadtman, E.R., The Effects of Citrate and Coenzyme A on Fatty Acid Metabolism, J. Biol. Chem. 222, (1956).

17. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NC13
SERIAL NUMBER

2. NINDB
INSTITUTE

3. Neurochemistry
LABORATORY

4. Intermediary Metabolism
SECTION

5. Bethesda, Maryland
LOCATION

6. Organization of the section
PROJECT TITLE

7. Roscoe O. Brady, Jr. (Acting)
PRINCIPAL INVESTIGATOR

8. ---
OTHER INVESTIGATORS

9. None

10. PROJECT DESCRIPTION

The intermediary metabolism of carbohydrates and amino acids as they involve the nervous system represents an important area not encompassed by the Section on Lipid Metabolism and the rest of the laboratory. The project has been devoted to planning, discussions with prospective personnel, and the purchase of standard, minimal equipment upon which the more specialized growth of the section may be built.

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Part B: Budget Data

11. NINDB-NC13
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	18,000	27,653	105,653	2.00	1.50	3.50
	BUDGETED POSITIONS			PATIENT DAYS		
	PROF	OTHER	TOTAL			
FY'57	8.00	6.00	14.00	—		

13. BUDGET ACTIVITY: RESEARCH

14. None

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP1
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Laboratory of Neurophysiology
LABORATORY

4. Special Senses
SECTION

5. Marine Biological Laboratory
Woods Hole, Massachusetts
LOCATION (IF OTHER THAN BETHESDA)

6. Analysis of impulse transmission in the squid giant synapse.
PROJECT TITLE

7. I. Tasaki
PRINCIPAL INVESTIGATOR

8. S. Hagiwara
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

0. PROJECT DESCRIPTION:

Objective: In the stellate ganglion of the squid, there is a large synapse (0.1 mm X 1 mm) which connects the giant presynaptic fiber (100μ in diameter) with the giant postsynaptic fiber (300μ in diameter). The purpose of this project is to clarify the mechanism of impulse transmission across this giant synapse.

Methods Employed: Isolated giant synapse preparations were made by the technique described by T.H. Bullock. The methods for measurement of the electrical properties of the synapse were developed by Tasaki and Hagiwara. Using two to three intracellular electrodes (metal wire or glass pipette), simultaneous recording of the action potentials and synaptic potentials from the pre- and post-synaptic fibers were made. The conductance of the synaptic membrane was investigated using the voltage clamp and A.C. impedance method.

Major Findings: 1. The temperature dependence of the synaptic delay was determined. 2. A slight change in the membrane action potential of the presynaptic fiber (caused by D.C. polarization) was found to affect the size of the synaptic potential to a remarkable extent. 3. By the method of voltage clamp, the intensity of the synaptic current (responsible for generation of the synaptic

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (Continued) NINDB-NP1
SERIAL NUMBER

potential) was determined. 4. It was shown that the synaptic transmission is not mediated by the action current from the presynaptic fiber; the time course of the observed synaptic potential was reproduced by a solution of the diffusion equation under appropriate boundary conditions.

Significance to Neurology Research: The complexity of the function of the central nervous system derives mainly from the interaction of neurones at excitatory and inhibitory synapses. It is hoped that this investigation will help us to understand the function of the central nervous system under normal as well as abnormal conditions.

Proposed Course of Project: The next step of this investigation will be to clarify the origin of the synaptic current. By the method of impedance bridge, a careful measurement of the membrane conductance will be made to determine the time course of the impedance-loss associated with the synaptic potential. Attempts will be made to examine whether or not there is an inhibitory afferent innervation in this giant synapse.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP1
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
~~$20,413~~	7,247	$27,660	1.00	.25	1.25

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
1.00	.25	1.25	—

13. BUDGET ACTIVITY:

RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP2
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE OR DIVISION

3. Laboratory of Neurophysiology
LABORATORY

4. Special Senses
SECTION

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Investigation of the function of the cochlea
PROJECT TITLE

7. Ichiji Tasaki
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

Objectives: This investigation is to clarify the process of initiation of nerve impulses in the cochlea by sound stimuli.

Methods Employed: The following methods developed mainly by the principal investigator were employed: (1) method of exposing the cochlea of the guinea pig, (2) method of introducing microelectrodes into the cochlea, and (3) method of injecting chemicals into the cochlea.

Major Findings: The effect of azide, diamox, cyanide, etc. into the endolymphatic space was investigated. Following injection of azide and cyanide, there was an immediate reduction in the endocochlear potential. Diamox and several monovalent cations did not have an immediate effect. The effect of anoxia upon the endocochlear response was reinvestigated; the reversible reduction of the steady potential was confirmed. The spread of electricity in the cochlea was investigated; the extent of spread of A.C. and D.C. was found to be far smaller than what has been assumed by several previous workers.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (Continued) NINDB-NP2
SERIAL NUMBER

Significance to Neurology Research: This investigation contributes to the understanding of the function of the normal as well as the abnormal ear.

Proposed Course of Project: When the sound-proof room in Building 9 is available, a further investigation on the endocochlear potential and on the physiological function of the efferent bundle of Rasmussen will be carried out.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP2
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$~~9,993~~	3,547	$13,540	.33	.25	.58

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.33	.25	.58	

13. BUDGET ACTIVITY:

RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB-NP2
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Hearing" by I. Tasaki, Accepted for publication in Ann. Rev. Physiol., 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

I. Tasaki was invited to write a review for the Annual Reviews of Physiology.

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP3
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE

3. Laboratory of Neurophysiology
LABORATORY

4. Special Senses
SECTION

5. Marine Biological Laboratory, Woods Hole, Mass. and Bethesda, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Analysis of the mechanism of action potential production in the nerve fiber.
PROJECT TITLE

7. I. Tasaki
PRINCIPAL INVESTIGATOR

8. S. Hagiwara
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

NINDB-NC3 and NINDB-B1

10. PROJECT DESCRIPTION:

Objectives: The purpose of this investigation is to clarify the mechanism whereby action potentials are produced in various excitable tissues: the myelinated nerve fiber, the vertebrate skeletal muscle fiber, and the invertebrate axons.

Methods Employed: Depending upon the type of material used and upon the type of measurements required, one of the following methods was used. 1. Single fiber techniques for studying the properties of the vertebrate myelinated nerve fiber. 2. The method of using multiple intracellular electrodes for studying the action potential of the frog skeletal muscle fiber. 3. The method of multiple intracellular electrodes for studying the response of the squid axon. 4. The method of A.C. impedance measurement and the method of voltage clamp for studying the conductance of the squid axon membrane. 5. The method of intracellular injection for studying the effects of various chemicals on the properties of the squid axon.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (Continued) NINDB-NP3
SERIAL NUMBER

Major Findings: It was possible to abolish the action potential of a single node and of a squid axon (under tetraethylammonium) in all-or-none manner by passing short pulses of inward currents. A hypothesis was advanced that initiation and abolition of an action potential is the result of "transition" of the membrane between the "two-stable states". A systematic investigation of the effects of various chemicals injected into the squid giant axon has been carried out. The role of the huge membrane capacity in the skeletal muscle fiber has been investigated.

Significance to Neurology Research: This investigation is expected to contribute to the understanding of the normal function of the nervous system.

Proposed Course of Project: The main course of investigation of this project is to clarify the relation between the "two-stable state hypothesis" and the sodium theory (Hodgkin and Huxley). A serious difficulty has been encountered in the attempt to explain the experimental results obtained by Tasaki and Hagiwara in terms of the sodium theory. Several crucial experiments are now being planned to test the validity of the sodium theory in the squid giant axon. An approach to the problem from an entirely different angle, namely, an attempt to detect U.V. absorption associated with an action potential, will be made during the next calendar year.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP3
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	4,829		$18,434	.67	-	.67

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.67	-	.67	—

13. BUDGET ACTIVITY:

RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB-NP3
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Initiation and abolition of the action potential of a single node of ranvier." I. Tasaki, J. Gen. Physiol. 39, 377-395, 1956.

"The effects of temperature and pressure upon the nerve fiber." I. Tasaki and C. S. Spyropoulos. To be published in a book entitled "The Effect of Temperature Upon Biological Systems"

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Dr. Tasaki was invited, together with Dr. Spyropoulos, to attend a symposium on "The Effect of Temperature upon Biological Systems", August 1956.

Dr. Tasaki was invited to write a chapter on Nervous Conduction for the "Handbook of Physiology".

Dr. Tasaki was appointed an Associate Member of the Academy of Neurology.

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP4
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE

3. Laboratory of Neurophysiology
LABORATORY

4. Special Senses
SECTION

5. Marine Biological Laboratory
Woods Hole, Massachusetts
LOCATION (IF OTHER THAN BETHESDA)

6. Experimental studies on nervous conduction along branching fibers.
PROJECT TITLE

7. Constantine S. Spyropoulos
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

Objectives: It is well known that nerve fibers divide into many smaller fibers near sensory and motor endings as well as in the central nervous system. At present there are no experimental studies on the behavior of nerve impulses at these points of branching. The objective of this investigation is to clarify; (1) the safety factor for nerve conduction at branching points, (2) whether there is a delay in conduction across these points, and (3) whether the nerve impulse travels in both directions in the same manner or whether there is a marked assymmetry in the behavior of the impulses with respect to direction of conduction

Methods Employed: A preliminary experiment was made on the squid giant axons using extracellular recording electrodes. In this animal it was possible to obtain axons with branches of various sizes. It is planned to improve the technique so as to allow recording of intracellular potentials at the junctional regions.

Major Findings: The preliminary experiment done in the Marine Biological Laboratory, Woods Hole, Massachusetts, indicated that there was a considerable delay in conduction of a nerve impulse from a small branch to the large (parent) axon; the delay was sometimes as much as 0.3 msec. So far no preparation has been encountered

Part A. Project Description Sheet (Continued)

NINDB-NP4
SERIAL NUMBER

in which impulses travelled in one direction across the junctional region but not in the other.

Significance to Neurology Research: It is hoped that this investigation may contribute to the understanding of the normal function of the nervous system.

Proposed Course of Project: An attempt will be made to explore the possibility of carrying out similar experiments on vertebrate nerve fibers. It is planned to complete this investigation in the period between June and August 1957 in the Marine Biological Laboratory, Woods Hole, Massachusetts.

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INDIVIDUAL PREJECT REPORT

Part B: Budget Data

11. NINDB-NP4
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	[redacted] 5,526	1,961	$7,487	.33	.25	.58

	BUDGETED POSITIONS			
	PROF	OTHER	TOTAL	PATIENT DAYS
FY'57	.33	.25	.58	—

13. BUDGET ACTIVITY:

RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S):

None

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP5
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE

3. Laboratory of Neurophysiology
LABORATORY

4. Special Senses Section
SECTION

5. Marine Biological Laboratory, Woods Hole, Mass. and Bethesda, Maryland
LOCATION (IF OTHER THAN BETHESDA)

6. Investigation of the effects of changes in temperature and pressure upon nervous activity.
PROJECT TITLE

7. Constantine S. Spyropoulos
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

NONE.

10. PROJECT DESCRIPTION:

Objectives: The effects of changes in temperature and pressure have been investigated in several biological systems (i.e., muscles, and bioluminescent systems). These studies have contributed to the understanding of the underlying biochemical processes. The objective of this investigation is to apply this method of changing the pressure and temperature under various chemical environments to the studies of the function of the nervous system.

Methods Employed: A special chamber was constructed to carry out various electrophysiological studies under high hydrostatic pressure. Single fiber techniques were employed for the studies on vertebrate myelinated nerve fibers and the intracellular recording techniques for the studies on the invertebrate axons.

Major Findings: The following properties of the nerve fiber have been investigated under various temperatures and pressures: membrane action potential, longitudinal action current, membrane impedance during activity, conduction velocity, resistance and capacity of the resting membrane, voltage-current relation (revealed by the voltage clamp technique), etc. One of the striking results

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (continued)

NINDB-NP5
SERIAL NUMBER

of these extensive studies is the finding that high hydrostatic pressures reversibly prolong the duration of the action potential (by a factor of 4 - 5 at 10,000 psi). Another interesting finding is that the narcotizing action of alcohol can be counteracted by lowering the temperature or by application of high pressure.

Significance to Neurology Research: The results obtained contribute to the understanding of processes underlying nervous activity. The finding that cooling and high pressure can counteract the narcotizing effect of some drugs may have some practical significance to anesthesiology.

Proposed Course of Project: It is planned to expand this investigation to include the interaction between temperature and pressure changes and the effect of various drugs known to act on the nervous system.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP5
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
			.33	.25	.58
FY'57 [redacted]		$7,487			

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
.33	.25	.58	—

13. BUDGET ACTIVITY:

Research

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

None.

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INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB-NP5
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"The effects of temperature and pressure upon the nerve fiber," by I. Tasaki and C. S. Spyropoulos. To be published in a book on THE EFFECT OF TEMPERATURE UPON BIOLOGICAL SYSTEMS.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

Spyropoulos was invited together with Tasaki to a symposium on "The effects of temperature upon biological systems," to present the data mentioned above. This was held at the University of Connecticut, August 1956.

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PUBLIC HEALTH SERVICE - - NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP6
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE

3. Laboratory of Neurophysiology
LABORATORY

4. Special Senses Section
SECTION

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Investigation of the electrical activity of the cardiac muscle.
PROJECT TITLE

7. Constantine S. Spyropoulos
PRINCIPAL INVESTIGATOR

8.
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

NONE.

10. PROJECT DESCRIPTION:

Objectives: The action potential of the heart muscle is known to have a peculiar "rectangular" configuration characterized by an initial peak followed by a long plateau. Recently, Spyropoulos has succeeded by prolonged repetitive stimulation in converting the ordinary triangular action potential of the nerve fiber into a rectangular configuration indistinguishable from that of the response of the heart. This finding indicates that the basic mechanism of action potential production may be common in the two excitable systems. The purpose of this investigation is to study the mechanism of production of the peculiar action potential in the cardiac muscle.

Method Employed: The method of intracellular recording of the action potential of the cardiac muscle was used.

Major Findings: (1) It was found that the rectangular response of the cardiac muscle can be converted into the triangular configuration by drugs which similarly affect the rectangular response of the nerve fiber. (2) Most of the chemicals affecting the rectangular response do not affect the triangular response. (3) Both in the cardiac muscle and in the nerve fiber, the temperature and pressure dependence of the rectangular response is different from that of the triangular response. (4) The duration of the

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (Continued) NINDB-NP6
SERIAL NUMBER

rectangular response of both the nerve fiber and the heart was found to be very unstable. (5) A working hypothesis has been postulated to the effect that the rectangular configuration of the cardiac response is related (as is the rectangular response of the nerve fiber) to the perpetual repetitive firing of impulses in the cardiac muscle.

Significance to Neurology Research: (1) It is hoped that this investigation will contribute to the understanding of the peculiar configuration of the action potential of the cardiac muscle. (2) This investigation may throw some light on the difference between a young heart and an old (aged) heart. (3) Many clinically and physiologically important chemicals such as acetylcholine, adrenaline, digitalis and curare affect the rectangular response of the heart or nerve fiber. Many of these chemicals convert the rectangular response into a triangular response. This investigation may contribute to the understanding of the action of these chemicals. (4) Stimulation of the vagus nerve is known to convert the rectangular response of the auricle of the heart into a triangularly shaped response. This investigation may contribute to the understanding of the vagal influence upon the heart.

Proposed Course of Project: It is planned to continue the search for differences and similarities between the rectangular response of the nerve fiber and that of the cardiac response. An attempt will be made to investigate the action potential of the embryonic heart muscle to determine if at some stage the response is triangular.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP6
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	[redacted]		$5,470	.34	-	.34

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	.34	-	.34	

13. BUDGET ACTIVITY:

Research

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO (S):

None.

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB-NP6
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Changes in the duration of the electric response of single nerve fibers following repetitive stimulation". C. S. Spyropoulos, J. Gen. Physiol., 40: 19-25, 1956.

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

None.

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Calendar Year 1956

PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP7
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE

3. Laboratory of Neurophysiology
LABORATORY

4. Spinal Cord
SECTION

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Origin of rhythmic activity in the spinal cord.
PROJECT TITLE

7. K. Frank and M. G. F. Fuortes
PRINCIPAL INVESTIGATORS

8. M. Becker and R. Morrell
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO.(S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

Objectives: To determine the mechanism of production of rhythmic activity of single cells in the spinal cord.

Methods Employed: Intracellular recording of electrical potentials across the membrane of a nerve cell. 1. Studies of excitability changes during rhythmic activity elicited by synaptic depolarization and by direct depolarization through the microelectrode. 2. Changes in ionic composition of the cytoplasm and drugs delivered just outside the cell may produce revealing changes in rhythmic activity.

Major Findings: Results reported last year on this study have been extended as follows: 1. There is good reason now to believe that a sensitive target area of the motoneurone, probably in the neighborhood of the axon hillock, is the actual site of origin of rhythmic firing. Depolarization of this area to threshold appears to be by spread of synaptic depolarization from other parts of the cell. 2. Trains of nerve impulses initiated in this target area travel out the axon but need not necessarily invade the rest of the cell. 3. Spinal motoneurones show only very limited accommodation to sustained depolarizing currents through intracellular electrodes and therefore probably also to a normal asynchronous afferent barrage.

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (Continued)

NINDB-NP7
SERIAL NUMBER

Significance to Neurology Research: Elucidation of the basic mechanisms of repetitive firing in normal nerve cells may provide leads for determining the etiology of diseases of the nervous system.

Proposed Course of Project: Emphasis during the coming year will be on direct excitability measurements during repetitive firing. It is hoped that substances can be introduced through the microelectrode, either intracellularly or just extracellularly which will further elucidate the rhythmic mechanisms. This work is considered to be a part of the main project of the section, Serial No. NINDB-NP8 and will no longer be carried as a separate project.

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INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP7
SERIAL NUMBER

12. BUDGET DATA:

ESTIMATED OBLIGATIONS			MAN YEARS		
DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57					
$[redacted]13,769		6,805 $21,974	.75	1.00	1.75

BUDGETED POSITIONS			PATIENT DAYS
PROF	OTHER	TOTAL	
FY'57			
1.00	2.00	3.00	—

13. BUDGET ACTIVITY:

RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

This is a cooperative project carried out in part with Dr. M. G. F. Fuortes of the research staff of the Army Medical School at Walter Reed Hospital.

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet

1. NINDB-NP8
SERIAL NUMBER

2. Neurological Diseases and Blindness
INSTITUTE

3. Laboratory of Neurophysiology
LABORATORY

4. Spinal Cord
SECTION

5.
LOCATION (IF OTHER THAN BETHESDA)

6. Mechanisms of interaction between neurones in the spinal cord.
PROJECT TITLE

7. [redacted]k and M. G. F. Fuortes
PRINCIPAL INVESTIGATOR

8. Mary Becker
OTHER INVESTIGATORS

9. IF THIS PROJECT RESEMBLES, COMPLEMENTS, OR PARALLELS RESEARCH DONE ELSEWHERE IN THE PUBLIC HEALTH SERVICE (WITHOUT INTERCHANGE OF PERSONNEL, FACILITIES OR FUNDS), IDENTIFY SUCH RESEARCH: (BY SERIAL NO. (S) IF WITHIN NIH).

None

10. PROJECT DESCRIPTION:

Objectives: The broad objective of this main project of the Spinal Cord Section is the investigation of basic mechanisms of neuronal interaction of the central nervous system operating in the spinal cord. Pursuit of this objective has led to the need for more exact information regarding the electrical properties of spinal motoneurones and the steps by which their action potentials are generated.

Methods Employed: Intracellular microelectrodes are used to stimulate and record from single nerve cells.

Major Findings: A. Studies of the electrical properties of spinal motoneurones yielded the following results: Average rheobasic stimulating current 7.4 X 10^{-9} A; membrane resistance by two indirect methods was 1.65 MΩ, threshold depolarization is slightly greater for direct than for synaptic excitation (1 mV); time constant by several methods was about 1 msec. These and other measurements have led to the conclusion that despite statements to the contrary it is unnecessary to assume that impinging afferent nerve impulses evoke motoneurone firing by any process other than by depolarization of the cell membrane to a critical level. Further, it is considered likely that the long time course of the synaptic potential produced by a single monosynaptic volley reflects the time course of a chemical mediator action and is not due to the

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INDIVIDUAL PROJECT REPORT

Part A. Project Description Sheet (Continued) NINDB-NP8
SERIAL NUMBER

passive reaction of the post-synaptic membrane. B. The motoneurone membrane shows evidence of two thresholds for electrical stimulation. This has been interpreted as indicating that there are two parts of the cell membrane having different properties. Studies have been made on each of these regions firing in isolation. It has been clearly demonstrated that activity in the smaller, sensitive region alone initiates a normal impulse in the motor nerve fiber regardless of invasion of the larger remaining portions of the motoneurone.

Significance to Neurology Research: Fundamental neurophysiological research designed to promote a better understanding of basic mechanisms operating in both the normal and the pathological central nervous system.

Proposed Course of Project: It is planned to continue this project indefinitely or as long as the techniques employed and proposed continue to yield significant results. Phases planned for work this year are: 1. Excitability changes during inhibition and during mixed inhibitory and excitatory volleys. 2. Identification of exact microelectrode position. 3. The effects of changes in chemical environment of the penetrated nerve cell. In addition, the project on repetitive activity of motoneurones will be combined with this project hereafter.

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part B: Budget Data

11. NINDB-NP8
SERIAL NUMBER

12. BUDGET DATA:

	ESTIMATED OBLIGATIONS			MAN YEARS		
	DIRECT	REIMBURSEMENT	TOTAL	PROF	OTHER	TOTAL
FY'57	[redacted]			1.50	2.25	3.75
	$31,431	14,173	$45,604			

	BUDGETED POSITIONS			PATIENT DAYS
	PROF	OTHER	TOTAL	
FY'57	2.00	2.00	4.00	-

13. BUDGET ACTIVITY:

RESEARCH

14. IDENTIFY ANY COOPERATING UNITS OF THE PUBLIC HEALTH SERVICE, OR OTHER ORGANIZATIONS, PROVIDING FUNDS, FACILITIES, OR PERSONNEL FOR THIS PROJECT IN FY 1957. IF COOPERATING UNIT IS WITHIN NIH INDICATE SERIAL NO(S):

This is a cooperative project carried out in part with Dr. M. G. F. Fuortes of the research staff of the Army Medical School at Walter Reed Hospital. Dr. Fuortes has now joined the staff at NINDB and plans to spend a part of his time cooperating on this project.

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PUBLIC HEALTH SERVICE -- NATIONAL INSTITUTES OF HEALTH

INDIVIDUAL PROJECT REPORT

Part C: Honors, Awards and Publications

15. NINDB-NP8
SERIAL NUMBER

16. LIST PUBLICATIONS OTHER THAN ABSTRACTS FROM THIS PROJECT DURING CALENDAR YEAR 1956:

"Stimulation of spinal motoneurones with intracellular electrodes." K. Frank and M.G.F. Fuortes, J. Physiol. (In press)

17. LIST HONORS AND AWARDS TO PERSONNEL RELATING TO THIS PROJECT DURING CALENDAR YEAR 1956:

2582

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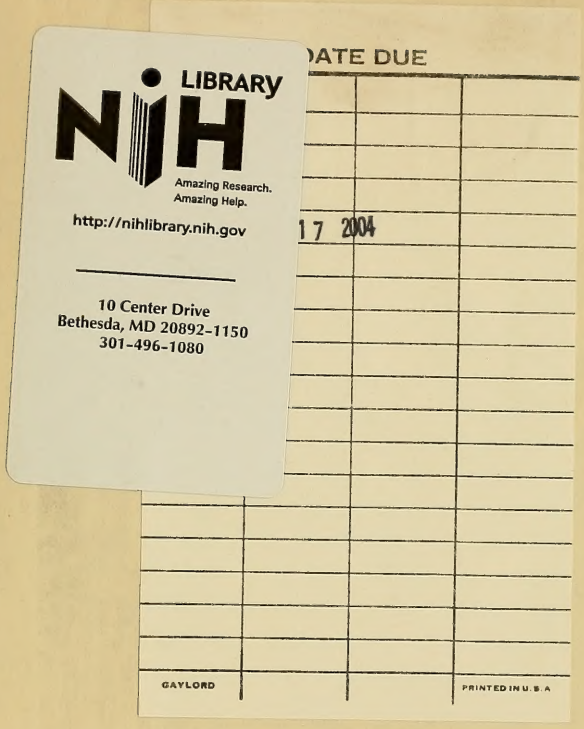

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